The chemistry of the **Cyclopropyl Group**

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Part 1

Edited by

ZVI RAPPOPORT

The Hebrew University, Jerusalem

1987

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The Chemistry of Functional Groups
Preface to the Series

The series 'The Chemistry of Functional Groups' is planned to cover in each volume all aspects of the chemistry of one of the important functional groups in organic chemistry. The emphasis is laid on the functional group treated and on the effects which it exerts on the chemical and physical properties, primarily in the immediate vicinity of the group in question and secondarily on the behaviour of the whole molecule. For instance, the volume *The Chemistry of the Ether Linkage* deals with reactions in which the C—O—C group is involved, as well as with the effects of the C—O—C group on the reactions of alkyl or aryl groups connected to the ether oxygen. It is the purpose of the volume to give a complete coverage of all properties and reactions of ethers in as far as these depend on the presence of the ether group but the primary subject matter is not the whole molecule, but the C—O—C functional group.

A further restriction in the treatment of the various functional groups in these volumes is that material included in easily and generally available secondary or tertiary sources, such as Chemical Reviews, Quarterly Reviews, Organic Reactions, various 'Advances' and 'Progress' series as well as textbooks (i.e. in books which are usually found in the chemical libraries of universities and research institutes) should not, as a rule, be repeated in detail, unless it is necessary for the balanced treatment of the subject. Therefore each of the authors is asked *not* to give an encyclopaedic coverage of his subject, but to concentrate on the most important recent development and mainly on material that has not been adequately covered by reviews or other secondary sources by the time of writing of the chapter, and to address himself to a reader who is assumed to be at a fairly advanced postgraduate level.

With these restrictions, it is realized that no plan can be devised for a volume that would give a *complete* coverage of the subject with *no* overlap between chapters, while at the same time preserving the readability of the text. The Editor set himself the goal of attaining *reasonable* coverage with *moderate* overlap, with a minimum of cross-references between the chapters of each volume. In this manner, sufficient freedom is given to each author to produce readable quasi-monographic chapters.

The general plan of each volume includes the following main sections:

(a) An introductory chapter dealing with the general and theoretical aspects of the group.

(b) One or more chapters dealing with the formation of the functional group in question, either from groups present in the molecule, or by introducing the new group directly or indirectly.

(c) Chapters describing the characterization and characteristics of the functional groups, i.e. a chapter dealing with qualitative and quantitative methods of determination including chemical and physical methods, ultraviolet, infrared, nuclear magnetic resonance and mass spectra: a chapter dealing with activating and directive effects exerted

by the group and/or a chapter on the basicity, acidity or complex-forming ability of the group (if applicable).

(d) Chapters on the reactions, transformations and rearrangements which the functional group can undergo, either alone or in conjunction with other reagents.

(e) Special topics which do not fit any of the above sections, such as photochemistry, radiation chemistry, biochemical formations and reactions. Depending on the nature of each functional group treated, these special topics may include short monographs on related functional groups on which no separate volume is planned (e.g. a chapter on 'Thioketones' is included in the volume *The Chemistry of the Carbonyl Group*, and a chapter on 'Ketenes' is included in the volume *The Chemistry of Alkenes*). In other cases certain compounds, though containing only the functional group of the title, may have special features so as to be best treated in a separate chapter, as e.g. 'Polyethers' in *The Chemistry of the Ether Linkage*, or 'Tetraaminoethylenes' in *The Chemistry of the Amino Group*.

This plan entails that the breadth, depth and thought-provoking nature of each chapter will differ with the views and inclinations of the author and the presentation will necessarily be somewhat uneven. Moreover, a serious problem is caused by authors who deliver their manuscript late or not at all. In order to overcome this problem at least to some extent, it was decided to publish certain volumes in several parts, without giving consideration to the originally planned logical order of the chapters. If after the appearance of the originally planned parts of a volume it is found that either owing to non-delivery of chapters, or to new developments in the subject, sufficient material has accumulated for publication of a supplementary volume, containing material on related functional groups, this will be done as soon as possible.

The overall plan of the volumes in the series 'The Chemistry of Functional Groups' includes the titles listed below:

The Chemistry of Alkenes (*two volumes*)
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The Chemistry of the Ether Linkage
The Chemistry of the Amino Group
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The Chemistry of the Sulphonium Group (two parts)
Supplement F: The Chemistry of Amino, Nitroso and Nitro Groups and their Derivatives (two parts)
The Chemistry of the Metal–Carbon Bond (four volumes)
The Chemistry of Peroxides
The Chemistry of Organic Se and Te Compounds Vol. 1
The Chemistry of Cyclopropyl group (two parts)

Titles in press:

The Chemistry of Organic Se and Te Compounds Vol. 2
The Chemistry of the Quinonoid Compounds
The Chemistry of the Sulphonium Group: Vol. 2
The Chemistry of Organo–Silicon Compounds

Advice or criticism regarding the plan and execution of this series will be welcomed by the Editor.

The publication of this series would never have started, let alone continued, without the support of many persons. First and foremost among these is Dr Arnold Weissberger, whose reassurance and trust encouraged me to tackle this task. The efficient and patient cooperation of several staff-members of the Publishers also rendered me invaluable aid (but unfortunately their code of ethics does not allow me to thank them by name). Many of my friends and colleagues in Israel and overseas helped me in the solution of various major and minor matters, and my thanks are due to all of them, especially to Professor Z. Rappoport. Carrying out such a long-range project would be quite impossible without the non-professional but none the less essential participation and partnership of my wife.

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SAUL PATAI

Contents

Foreword

The cyclopropyl group has enough special characteristics to distinguish it from other alkyl and cycloalkyl groups and we believe it deserves a special volume dealing with its chemistry. Two chapters related to this group appeared in previous volumes of the series. The similarities between cyclopropanes and olefins were discussed in a chapter on the "Olefinic properties of Cyclopropanes" in The Chemistry of Alkenes, Vol. 2 (1970) and "Dihalocyclopropanes" were described in Supplement D (1983) which deals with the carbon–halogen bond.

Only one chapter intended to appear in this volume, that on "Photochemistry of Cyclopropanes" was not delivered. Since progress in the field will undoubtedly result in development of new topics we hope to include this chapter and possibly others in a supplementary volume devoted to the cyclopropyl group in the future. We will be grateful to readers for proposals concerning missing topics and chapters which may be included in such a future volume, or who will bring mistakes in the present volume to our attention.

The literature coverage in this volume is mostly up to mid-1985 with some chapters containing also more recent references.

Jerusalem, January 1987 Zvi Rappoport

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CHAPTER 1

Structures, energies and spectra of cyclopropanes

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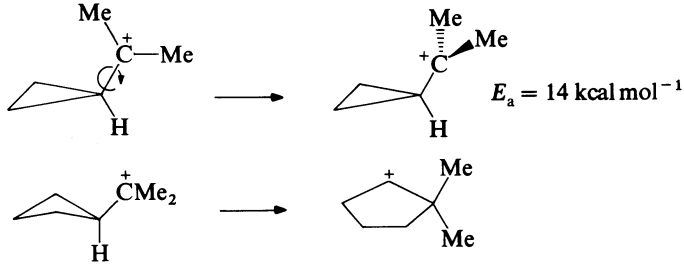
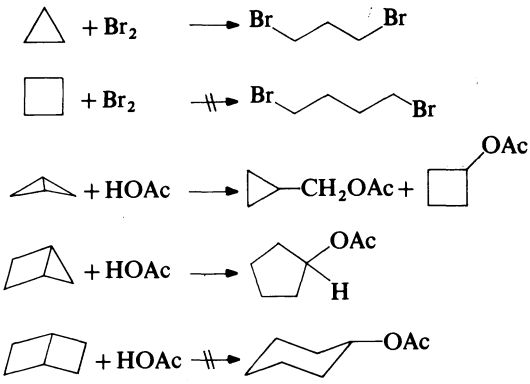
I. INTRODUCTION

Cyclopropane is unique among carbocycles in both its properties and reactions[1]. It can, for example, stabilize electron deficient centers to a much greater extent than cyclobutane or the larger carbocycles. Thus, the cyclopropyldimethylcarbinyl cation is unusually stable and has a large activation energy for rotation about the cyclopropyl-carbocation bond[2]. In contrast, the corresponding cyclobutyldimethylcarbinyl cation quickly rearranges to a cyclopentyl cation. Here, some strain relief occurs in the rearrangement, but this is opposed by the conversion of the tertiary carbocation to the less stable[3] secondary ion:



Similarly, cyclopropane reacts readily with electrophiles such as bromine, whereas cyclobutane and the larger carbocycles are inert. This carries over to the corresponding bicyclic compounds. Bicyclobutane is extraordinarily reactive towards electrophiles, bicyclo[2. 1.0]pentane has high reactivity, but bicyclo[2. 2.0]hexane is almost inert[4]. This does not correspond to differences in driving force for the reactions, in fact a reverse correlation is found!



In order to understand these and related differences between cyclopropane and other carbocycles, it is helpful first to consider the results of theoretical calculations. It is now possible to obtain high quality wave functions for cyclopropane and related molecules via ab initio molecular orbital calculations[6]. The most satisfactory way in which to examine these wave functions is by calculating the charge densities. It must be remembered that the molecular orbitals themselves are just convenient functions for solving the Schroedinger wave equation:

$$\lambda\psi = \alpha\psi$$

Here, λ is an operator appropriate to the quantity of interest, ψ is the wave function for the system being studied, and α is *the result of an experimental measurement.* Experimental quantities include the energy, the charge density, the momentum, the dipole moment, etc. The molecular orbitals and their energies are *not* experimental quantities and the wave function for a system need not be expressed in terms of molecular orbitals. In fact, the wave functions themselves would not be necessary if there were a direct way in which to calculate the electron density distribution for a molecule since all of the properties may be derived from the density[7].

The electron density distribution in the three-carbon plane of cyclopropane is shown in Figure 1(a). The total densities rarely are very informative because the high local concentrations near the nuclei dominate the distribution. However, we may subtract the density which would be appropriate for spherically averaged carbon atoms placed at the coordinates of the cyclopropane carbons. This will show how the electron density distribution has been affected by bond formation (Figure 1(b)). It has been called a deformation density plot[8].

The bonding regions in cyclopropane are now easily recognized as the regions of positive deformation density between the nuclei. In ordinary compounds the deformation density between a pair of bonded carbons is collinear with the conventional bond. In the case of cyclopropane, however, the deformation density lies outside of lines drawn between carbons, leading to the formation of bent bonds.

It is interesting to note that the idea of bent bonds for cyclopropanes was first proposed by Ingold in an effort to explain why tetrahedrane could be a stable molecule[9]! The bent

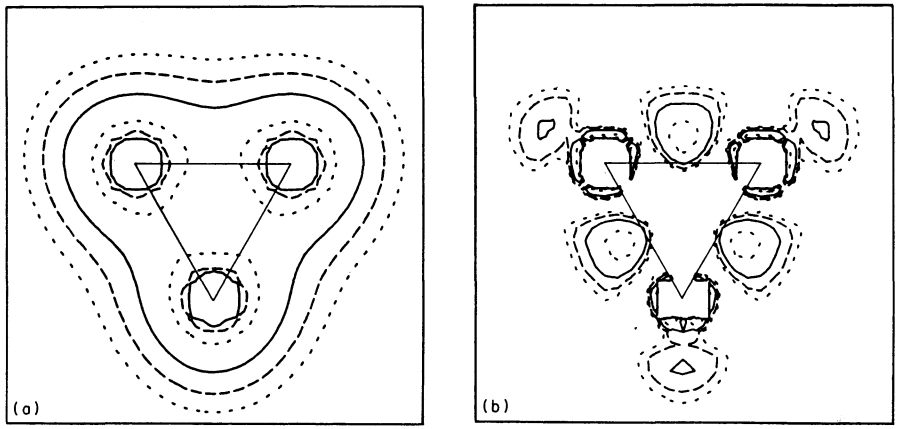
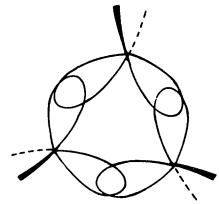


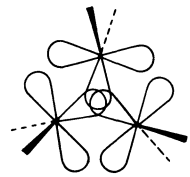
FIGURE 1. (a) Total electron density in the three-carbon plane of cyclopropane. (b) Regions of positive deformation density for cyclopropane (i. e. regions of greater electron density than would be expected for three carbon atoms)

character of the C–C bonds in cyclopropane was first recognized theoretically by Förster[10], and was developed in more detail by Coulson and Moffitt[11] who started with sp^3 hybridized carbons as a zeroth order model. From these hybrid orbitals one may readily construct appropriate two electron molecular orbitals[12].

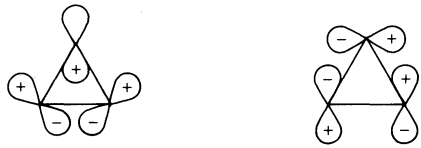


They recognized that the strongly bent bonds in this model would lead to relatively poor overlap and weak C–C bonds. A decrease in the s character of the C–C bonds and a consequent increase in s character of the C–H bonds would lead to less bent and stronger bonds, and an increase in the HCH angle. However, there was a limit to the decrease in s character because bonds formed from just p orbitals, although having desirable orientations (90° vs. 109.5° for sp^3), are weaker than those that have some s character. The best compromise was found with 20 % s and 80 % p character in the C–C bonds, and 30 % s and 70 % p character in the C–H bonds. This result is in good agreement with experimental studies which will be described below.

A second model is that of Walsh[13]. Here, the zeroth order model used sp^2 hybrid orbitals to form the CH bonds, with the C–C bonds formed using p orbitals along with the sp^2 orbitals pointing toward the center of the three-carbon unit. Again, the model predicts the



formation of bent bonds. It is, however, not possible to convert the Walsh orbitals to the bonding cannonical molecular orbitals via a unitary transformation[12]. Therefore, the Walsh description is not equivalent to the Förster–Coulson–Moffitt model, and is not a correct description of the ground state of cyclopropane. The degenerate pair of highest occupied molecular orbitals for cyclopropane are often referred to as Walsh orbitals, but this is not correct.



Is it possible to bypass these models, and determine the nature of the bonds directly from the charge density? Bader has developed a useful approach which defines both which pairs of atoms are joined by chemical bonds, and the nature of the bonds thus formed[14]. A characteristic of all chemical bonds is that they possess a bond critical point at which the electron density is a minimum along the path between the nuclei, and is a maximum in all direction perpendicular to that path. The path between the nuclei which contains the bond critical point, and maximizes the charge density throughout its length is known as the bond path.

In a simple molecule such as ethane, the bond path between the two carbons coincides with the conventional bond. In compounds having bond angle distortion, such as cyclopropane, the bond path deviates from the line of centers, leading to a bent bond (Figure 2). Whereas the calculated distance between carbons in cyclopropane is only 1.497 Å, the length along the bond path is 1.507 Å, which is significantly greater. The C–C–C bond angle may then be defined as the angle between the bond paths, and is 78.84° rather than the 60° angle between the lines of centers. The charge density at the bond critical point (ρ_b) has been found to be a useful indicator of the bond order, n:[14]

$$n = e^{-0.957(\rho_b - 0.256)}.$$

In n-butane, the value is 0.256 e/B^3 (B = Bohr = 0.529 Å) whereas in cyclopropane it is 0.249 e/B^3, leading to a C–C bond order of 0.99 for cyclopropane.

It would seem useful to compare these results with those for the other small ring carbocycle, cyclobutane (cf. Table 1). The C–C bond paths are shown in Figure 2, and have the angle between the bond paths of 95°, as compared to 89° for the conventional bond angle. The charge density at the bond critical point is 0.247 e/B^3 which is close to that for cyclopropane. Data for some other related compounds are summarized in Table 1. The structures of these and related compounds will be further considered below.

Small ring hydrocarbons and their derivatives are ideal subjects for theoretical studies since they are relatively small and are of special chemical interest. Theory becomes of particular value to chemists when its results may be compared with experimental measurements. The quantities which may be considered include:

A. Geometry.
B. Charge distribution.
C. Energies.
D. Bond strengths and force constants.
E. NMR spectra.
F. Interactions with electron deficient and unsaturated centers.
G. Electronic excitation.

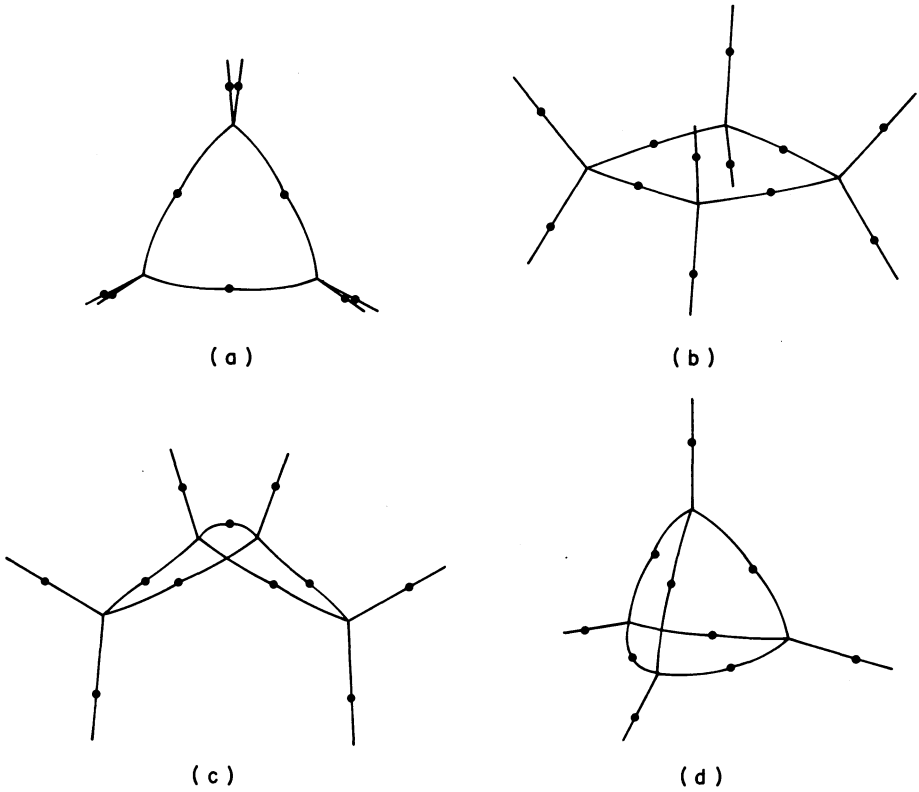


FIGURE 2 Molecular graphs for: (a) cyclopropane; (b) cyclobutane; (c) bicyclo[1.1.0]butane; and (d) tetrahedrane showing the bent carbon–carbon bonds. The solid circles show the bond critical points (Ref. 14)

A. Geometry

The geometries of most compounds may be estimated rather well via ab initio molecular orbital calculations[16]. Here, one starts with a guessed trial geometry, and calculates the forces acting on all of the atoms[17]. The atoms are then moved in directions which will reduce the forces, and the energy is recalculated. This is continued until the forces become negligible. The only variable in such a calculation is the choice of basis set—the set of atomic orbitals from which the wave functions will be constructed. Here, it is important to recognize that the 'size' of an atom varies with its environment. Therefore, one normally uses a split valence basis set in which the valence atomic orbitals are taken as pairs, one smaller and the other larger. The calculation will choose appropriate coefficients from each member of the pair to obtain an optimal size for the atom. A popular basis set of this type is designated as 3-21G[18]. Here three gaussian functions (with an e^{-r^2} distance dependence) are used to represent the core atomic orbital (1s on carbon), two are used for each inner valence atomic orbital, and one is used to represent each outer valence atomic orbital. The gaussian functions are used rather than employing hydrogen-like (e^{-r} distance dependence) atomic orbitals directly because the calculation of electron–electron repulsion

TABLE 1. Carbon–carbon bonding in cycloalkanes (6-31G*)[a,15]

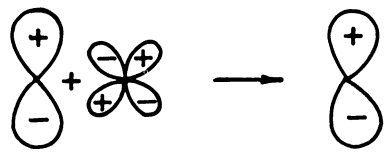
	Bond	r_{CC} (Å)	r for b path (Å)	ρ at r_{min}	Angle	Geometric(°)	Bond path(°)	Dev.
Cyclopropane	1, 2	1.497	1.507	0.249	123	60.00	78.84	18.8
Cyclobutane	1, 2	1.549	1.551	0.247	123	89.37	95.47	6.1
Cyclohexane	1, 2	1.534	1.534	0.253	123	111.37	110.01	−1.4
Bicyclo[1.1.0]butane	1, 2	1.488	1.496	0.254	123	59.06	72.44	13.4
	1, 3	1.467	1.482	0.249	312	60.47	76.33	15.9
					412	98.38	105.57	7.2
Bicyclo[2.1.0]pentane	1, 2	1.528	1.530	0.256	154	60.86	79.28	18.4
	2, 3	1.558	1.560	0.243	123	90.84	96.76	5.9
	1, 4	1.513	1.526	0.244	215	110.03	109.72	−0.3
	1, 5	1.494	1.503	0.253	145	59.57	78.30	18.7
Bicyclo[1.1.1]pentane	1, 2	1.546	1.551	0.246	123	74.40	84.70	10.3
					214	87.23	95.86	8.6
Spiropentane	1, 2	1.479	1.492	0.257	123	59.24	79.04	19.8
	2, 3	1.513	1.521	0.243	132	61.51	84.84	23.3
					134	137.60	123.02	−14.6
[1.1.1]Propellane	1, 2	1.502	1.511	0.252	123	61.81	59.37	−2.4
	1, 4	1.543	1.543	0.203	213	59.06	69.06	10.0
					215	95.58	107.99	12.0
Tetrahedrane	1, 2	1.463	1.484	0.255	123	60.00	81.36	21.4
Cubane	1, 2	1.563	1.568	0.244	123	90.00	97.43	7.4

[a] The structures were calculated using the 6-31G* basis set. The observed structures of some of these compounds are given in Table 2.

integrals is simplified when gaussian functions are used. Another common basis set is 4-31G[19] which uses four gaussians for the core atomic orbitals, three for the inner valence orbitals and one for the outer valence orbitals.

In the case of compounds with severe bond angle distortion, these basis sets are not adequate, and it becomes important to add polarization functions which allow the atomic orbitals to distort in such as fashion as to give improved bonding. In the case of carbon 2p orbitals, the polarization functions are d orbitals. It should be noted that these d orbitals serve only to deform the p orbitals, and there is no suggestion that carbon 'uses' d orbitals in forming bonds. A commonly employed basis set of this type is designated as 6-31G*[20]. Here six gaussians are used to form the inner (1s) orbital, three gaussians represent the inner valence orbitals, one is used for the outer valence orbitals, and the asterisks indicates that a set of d orbitals are added at carbon.

An illustration of how d orbitals polarize p orbitals is shown below. The d orbital enhances the p function on the right hand side where the phases of the two orbitals match,



and it diminishes it at the left side where the phases are opposed. This results in a deformation of the p orbital which could lead to improved bonding.

The results of *ab initio* calculations using the 6-31G* basis set for a series of small ring hydrocarbons are shown in Table 2. It can be seen that the bond angles are generally predicted with good accuracy[16]. The calculated bond lengths are invariably smaller than the observed values. This arises from two factors. First, the stretching vibrations in most molecules are anharmonic, with bond stretching being energetically somewhat easier than bond compression. All molecules vibrate at the zero point level, and as a result the average length at this level will be slightly longer than the distance corresponding to the bottom of the potential well (Figure 3).

A second factor is the neglect of electron correlation. In a conventional ab initio procedure, electron repulsion is calculated as the repulsion between 'smeared out'

TABLE 2. 6-31G* Energies and structures for hydrocarbons[a]

Compound	Energy (hartrees)	Bond	Calc. (Å)	Obs. (Å)	Angle	Calc. (°)	Obs. (°)
Hydrogen	−1.12683	H–H	0.730	0.740			
Methane	−40.19517	C–H	1.084	1.094			
Ethane	−79.22876	C–C	1.527	1.532	HCH	107.7	107.3 ± 0.3
		C–H	1.086	1.102			
Propane	−118.26365	C–C	1.528	1.526	CCC	112.7	112.4 ± 0.2
		C_1H	1.087	1.092	HC_2H	106.3	106.1 ± 0.2
		C_2H	1.086	1.096			
Cyclopropane	−117.05887	C–C	1.497	1.512	HCH	114.2	114.0 ± 0.7
		C–H	1.076	1.083			
Cyclobutane	−156.09703	C–C	1.548	1.555	CCC	89.0	~ 87.2
		C–H	1.082	1.090	HCH	108.2	—
Cyclohexane	−234.20796	C–C	1.533	1.535	CCC	111.4	111.4 ± 0.2
		C–H	1.088	1.102	HCH	106.8	107.5 ± 1.5
Bicyclobutane	−154.87169	C_1C_3	1.466	1.497	$C_1C_2C_3$	58.9	60.0
		C_2C_3	1.502	1.498	HC_2H	114.0	115.6 ± 1.2
		C_1H	1.070	1.071			
		C_2H	1.080	1.093			
Ethylene	−78.03172	C–C	1.317	1.339	HCH	116.4	117.8 ± 0.3
		C–H	1.076	1.085			
Cyclopropene	−115.82305	C_1C_2	1.276	1.296	C_2C_1H	150.2	149.9 ± 0.1
		C_1C_3	1.495	1.509	HC_3H	112.9	114.6 ± 0.2
		C_1H	1.068	1.072			
		C_3H	1.083	1.088			
Cyclobutene	−154.89962	C_1C_2	1.322	1.342	$C_1C_2C_3$	94.5	94.2 ± 0.3
		C_2C_3	1.517	1.517	$C_2C_3C_4$	85.5	85.8 ± 0.2
		C_3C_4	1.562	1.566	HC_3H	108.5	109.2 ± 0.5
		C_1H	1.070	1.083			
		C_3H	1.085	1.094			

[a] The experimental data were taken from *Landolt-Bornstein, New Series, Group II*, Vol. 7, Springer Verlag, Berlin, 1976. The calculated geometries were taken from K. B. Wiberg and J. J. Wendoloski, *J. Am. Chem. Soc.*, **104**, 5679 (1982) and K. B. Wiberg, *J. Am. Chem. Soc.*, **105**, 1227 (1983).

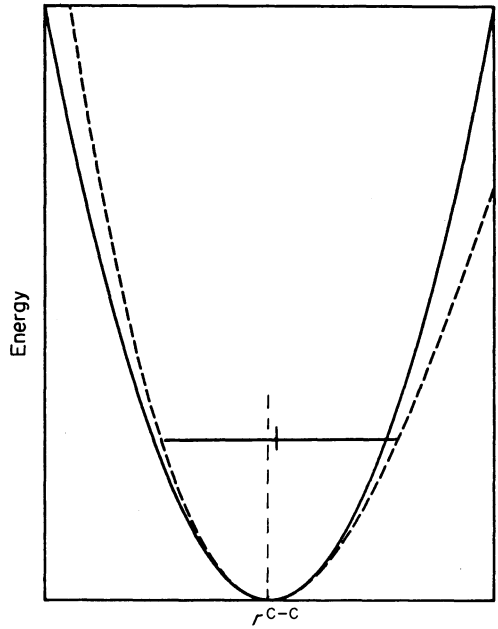


FIGURE 3. The solid line is a harmonic potential function, and the dashed line is a typical anharmonic function. The horizontal line represents the zero-point vibrational energy level, and the average value of r is shown. It is larger than the equilibrium value of r (vertical dashed line)

distributions for a given pair of electrons. This will overestimate the electron repulsion since electrons will tend to stay out of each other's way, i.e. their motions are correlated. Correction for electron correlation tends to make charge distributions in the bonding region somewhat more diffuse, and results in a small lengthening of C–C bonds. The relationship between the calculated and observed C–C bond lengths for hydrocarbons has been examined for three commonly used basis sets and has led to the following expressions[21]:

$$r_{CC}(\text{3-21G}) = 1.120 r_{CC}(\text{obs}) - 0.176 \quad \text{std. dev.} = 0.013 \quad R = 0.996$$
$$r_{CC}(\text{4-31G}) = 1.073 r_{CC}(\text{obs}) - 0.113 \quad \text{std. dev.} = 0.011 \quad R = 0.997$$
$$r_{CC}(\text{6-31G*}) = 1.064 r_{CC}(\text{obs}) - 0.102 \quad \text{std. dev.} = 0.012 \quad R = 0.996$$

It can be seen that in each case, the standard deviation is quite small, in the order of 0.01 Å. This is comparable to the experimental uncertainty in the measurements (generally ~ 0.005 Å).

The ability to calculate geometries with satisfactory accuracy becomes of special significance in considerations of compounds which have not as yet been prepared. Once the optimized geometry has been found, one is in a position to estimate the heat of formation, vibrational spectrum, and other properties. These data are useful in trying to decide whether or not the compound is likely to be stable, and in its identification[22].

As noted above, with these small ring compounds one must distinguish between the geometrical bond angles and the angles between bond paths. Spiropentane provides a useful illustration. The central carbon forms four identical bonds and therefore must use orbitals which may be described as sp^3. Thus, although the geometrical angle at the central carbon is about the same as for cyclopropane, the angle between the bond paths (84.8°) is considerably larger than that for cyclopropane (78.8°). Tetrahedrane has a similar problem, and here, the angle between bond paths is 81.4°.

Both the C–C and C–H bonds in cyclopropanes normally are shorter than those in other cycloalkanes such as cyclohexane. The shorter C–C bonds are due at least in part to their bent nature, and the shorter C–H bonds are due to the larger than normal s character in these bonds. This also is seen in related compounds such as bicyclobutane where the bridgehead C–H bond is one of the shortest of saturated CH bonds, and as will be discussed below, it has one of the largest percentages of character (% s character) among these compounds.

B. Charge Distribution

Another quantity which may be examined theoretically is the charge distribution. Experimentally, this may be determined from an analysis of X-ray crystallographic data, particularly if they were obtained at low temperatures so as to minimize thermal motion, and if data were taken to relatively large angles. The result of any analysis of X-ray data is an electron density map, and the locations of atoms are inferred from the observations of regions of high electron density. If the data are suitably obtained, the electron density map will be of sufficient accuracy to be compared with the calculated maps, and in all cases studied, the two are in excellent agreement[23]. The experimental map for a [3.1.1]propellane derivative[24] is shown in Figure 4, and the bent bonds to the methylene group in the cyclopropane ring are easily seen. The central bond has essentially no deformation density. This does not indicate the absence of a bond, but rather that the electron density in this region is only 75% that of a normal C–C bond.

It would be interesting to be able to assign electron populations to the atoms in a molecule, or at least to have a way in which to see how electron densities change as a result of the introduction of substituents. In the latter case, an electron density difference map can be quite revealing. However, it does not provide a ready means for giving quantitative expressions for population changes, and is not useful for giving absolute values for populations.

The Mulliken population analysis has commonly been used to obtain electron populations[25]. It sums the populations corresponding to the atomic orbitals which 'belong' to a given atom, and divides the electron population in the bonding region between the atoms involved. However, as pointed out above, atomic orbitals should not be considered to 'belong' to atoms once they have been used to form molecular orbitals. A more general way is to assign a region of space to each atom in a molecule, and to integrate the charge density for this region[26].

If one starts at the bond critical point (cf. introduction), one may develop paths of maximum rate of decrease of electron density. The network of these paths starting at all angles with respect to the bond provides a partitioning surface separating a given pair of atoms. Integration of the charge density (obtained from the wave functions) over the volume assigned to a given atom provides the electron population. In the case of methane, using the well balanced 6-31G** basis set (i.e. d orbitals at carbon and p orbitals at hydrogen) the electron population at the hydrogen of methane was found to be $1.065e^{27}$. This corresponds to a bond dipole in the sense C^+–H^-, and is found with all hydrocarbons which have been examined except acetylene[27]. Typical values for some hydrocarbons are given in Table 3.

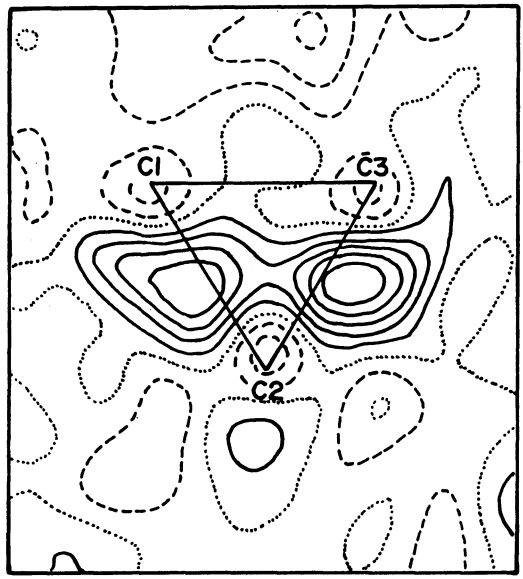


FIGURE 4. Experimental deformation density curve for a [3.1.1]propellane derivative. The C(1)–C(3) bond is the central bond. Note the bent C(1)–C(2) and C(2)–C(3) bonds. Taken from Ref. 24 with permission of the American Chemical Society

TABLE 3. Electron populations at hydrogens (6-31G**)[15]

Compound	Population
Methane	1.065
Ethane	1.082
Ethylene	1.044
Acetylene	0.883
Cyclopropane	1.052
Cyclobutane	1.076
Cyclohexane	1.094
Bicyclobutane	1.005 (CH) 1.054 (CH_2)

On the basis of the Förster–Coulson–Moffitt model for cyclopropane, for its CH bonds, one would expect the carbon to use an orbital with more s character than in methane, and therefore it would be more electronegative, giving a smaller electron population at hydrogen. This is just what is found. The normal value for methylene hydrogens is $\sim$ 1.094e (cyclohexane, CH_2 of *n*-pentane). The population for the cyclopropane hydrogens is closer to that of ethylene than this normal value. Among the saturated compounds, the population is smallest at the bridgehead of bicyclobutane, and here markedly increased acidity is noted[28]. It may also be noted that there is a fairly good

correlation between the populations and the calculated bond lengths:

$$\text{Population} = 4.39 r_{CH}(\text{6-31G*}) - 3.68 \qquad R = 0.962$$

It will be shown that the vibrational frequencies and NMR ^{13}C–H coupling constants also are related to the CH bond lengths.

The dipole moment is a manifestation of the overall charge distribution, and the calculated moments are generally in good agreement with the experimental values. Among cyclopropene derivatives, cyclopropene is the most interesting case. Here, the sign of the dipole moment is reversed from that found in cyclobutene or other cycloalkenes[29]. The

$\mu = -0.454$ $\mu = 0.132$

sign for cyclobutene is easily explained as being due to the higher electronegativity of the sp^2 carbons at the double bond as compared to the sp^3 methylene carbons. In cyclopropene, the reversed dipole can be explained as arising from the mixing of the π MO with the out-of-plane p orbital at the methylene group[29].

C. Energies

The next quantities which may be examined are the energies. Here, the usual experimental quantity is the heat of formation which is derived from the heat of combustion. In the case of calculated energies, we obtain the total energies arising from the kinetic energy of the electrons, the nuclear-electron attractions, and the repulsions between electrons and between nuclei. They are usually given in atomic units (hartrees, 1 H = 627.5 kcal mol^{-1}). The principal difficulty in relating the two quantities is that the usual calculations neglect the correlation between the motions of the electrons, and as a result the electron repulsion terms are too large. This correlation energy must somehow be factored out. It is mainly related to the numbers and types of atoms involved, and may approximately be cancelled via the use of an isodesmic reaction[30] which is simply a balanced equation. The energy change for the process is calculated, and if the energies of all but one of the compounds are known, the unknown energy may be estimated from the calculated energy change. The number and types of bonds provide a significant but much smaller contribution to differences in correlation energy, and so it is usually more satisfactory to use a homoisodesmic reaction[31] in which the bonding also is maintained constant on both sides of the equation. As an example, consider cyclopropane:

$$+ 2CH_4 = CH_3CH_2CH_3 + CH_3CH_3$$

In this hypothetical reaction, cyclopropane is converted to simpler compounds, propane and ethane, via the reaction with methane. Using the calculated energies given in Table 2, we see that the energy change is predicted to be -27.1 kcal mol^{-1}. This energy must be corrected for the zero point energies of all of the compounds, and leads to a calculated $\Delta H_r = -22.6$ kcal mol^{-1} at 0 K. Addition of the energy changes on going from 0 K to 298 K (25°C) then leads to a predicted $\Delta H_r = -23.7$ kcal mol^{-1} at 25°C[32]. Using the known heats of formation of methane, ethane and propane, the predicted ΔH_f of cyclopropane is 14.4 kcal mol^{-1} which may be compared with the observed value of 12.7 kcal mol^{-1}. The heats of formation are usually estimated to within a few kcal mol^{-1} via this procedure using energies derived with the 6-31G* basis set.

Smaller basis sets give less satisfactory results, particularly with the more highly strained compounds.

This is a cumbersome procedure which requires knowledge of zero-point energies and heat capacities which are frequently not available. The use of homoisodesmic reactions is equivalent to a group equivalent scheme and may conveniently be replaced by one. In addition, both zero-point energies and the change in ΔH_f on going from 0 K to 298 K may be represented by group equivalents. Thus, an attempt was made to incorporate all three terms into a single equivalent for a given group[33]. The results are shown in Table 4 where the heat of formation is given by:

$$\Delta H_f = 627.5(E_T - n_{CH_3}E_{CH_3} - n_{CH_2}E_{CH_2} - \ldots)$$

Here 627.5 is the conversion factor from atomic units to kcal mol^{-1}, E_T is the calculated

TABLE 4. Calculated and observed heats of formation for hydrocarbons[21]

Compound	E (hartrees)	ΔH_f (kcal mol^{-1})		
		obs.	calc.	diff.
Ethane	−79.22876	−20.04	−20.10	0.06
Propane	−118.26365	−25.02	−25.29	0.27
Butane	−157.29840	−30.03	−30.39	0.36
Isobutane	−157.29896	−32.07	−31.61	−0.46
Pentane	−196.33302	−35.08	−35.41	0.33
Neopentane	−196.33383	−40.14	−38.55	−1.59
Cyclopropane	−117.05887	12.73	13.17	−0.44
Cyclobutane	−156.09703	6.78	5.94	0.84
Cyclopentane	−195.16124	−18.44	−17.65	−0.79
Cyclohexane	−234.20796	−29.50	−30.26	0.76
Bicyclo[1.1.0]butane	−154.87176	51.90	55.53	−3.63
Bicyclo[2.1.0]pentane	−193.92697	37.70	37.58	0.12
Bicyclo[2.2.0]hexane	−232.96520	29.90	30.30	−0.40
Bicyclo[2.2.1]heptane	−272.06115	−12.40	−13.19	0.79
Bicyclo[2.2.2]octane	−311.10358	−24.30	−23.12	−1.18
Spiropentane	−193.91752	44.20	42.62	1.58
Cubane	−307.39361	148.70	147.07	1.63
Ethylene	−78.03172	12.50	12.71	−0.21
Propene	−117.07147	4.88	3.92	0.96
1-Butene	−156.10487	−0.20	−0.33	0.13
cis-2-Butene	−156.10786	−1.86	−2.76	0.90
trans-2-Butene	−156.11041	−2.99	−4.36	1.37
Isobutene	−156.11058	−4.26	−5.49	1.23
2,3-Dimethyl-2-butene	−234.17689	−16.42	−15.80	−0.62
Cyclopropene	−115.82305	66.20	69.21	−3.01
Cyclobutene	−154.89962	37.45	37.87	−0.42
Cyclopentene	−193.97717	8.23	5.91	2.32
1,3-Butadiene	−154.91965	26.11	24.50	1.61
1,4-Pentadiene	−193.94093	25.30	27.86	−2.56
Cyclopentadiene	−192.79172	31.94	30.34	1.60
Norbornadiene	−269.65245	57.40	59.37	−1.97
Acetylene	−76.81783	54.34	54.56	−0.22
Propyne	−115.86432	44.39	44.25	0.14
1-Butyne	−154.89903	39.49	39.18	0.31
2-Butyne	−154.90925	34.71	34.93	−0.22

Rms error = 1.33.

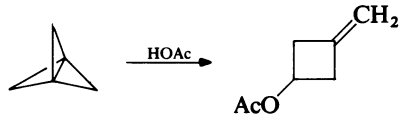
total energy using the 6-31G* basis set, n_{CH_3} is the number of methyl groups, and E_{CH_3} is the group equivalent for a methyl group in a hypothetical compound for which $\Delta H_f = 0.0$ (Table 5). The results can be seen to be quite satisfactory with an average error of only 1.3 kcal mol^{-1} [21]. Somewhat larger errors are found with other basis sets[21].

TABLE 5. Group equivalents[a]

Group	Value (hartrees)[b]
CH_3	−39.59836
CH_2	−39.02662
CH	−38.45350
C	−37.87895
CH_2	−39.02599
CH	−38.45336
C	−37.87913
CH	−38.45239
C	−37.88410

[a] For group equivalents for other groups and other basis sets see Ref. 21.
[b] 1 H = 627.5 kcal mol^{-1}.

One potential problem with any such correlation is that it may not predict good values of ΔH_f for compounds which were not included in the original test group. It is found, for example, that the energies of conjugated aromatic systems are not well reproduced, probably because of a difference in correlation energy between normal π bonds and delocalized π bonds[23]. Among non-aromatic compounds, [1.1.1]propellane (**1**) is a particularly distorted cyclopropane, and should provide a good test. Its ΔH_f was estimated to be 89 kcal mol^{-1}. An experimental value was obtained by measuring the heat of its

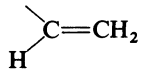
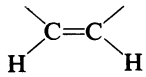
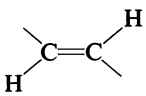
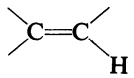
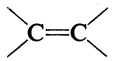


$\Delta H = -35.2$ kcal mol^{-1}

(**1**)

reaction with acetic acid[34]. From this, $\Delta H_f = 84$ kcal mol^{-1} is derived for the propellane. The error is in the same direction as for bicyclobutane and is somewhat larger, but still represents quite good agreement considering the unusual nature of **1**. One may therefore have confidence that less strained compounds will have their heats of formation estimated satisfactorily. The results for a number of cyclopropanes and related small ring hydrocarbons are shown in Table 6.

The heats of formation are not convenient quantities for comparing compounds having different numbers of carbons. Here, the strain energies are much more useful. The simplest definition is the difference between the observed ΔH_f and that calculated using a strain-free model. In the case of cyclopropane, $\Delta H_f = 12.73$ kcal mol^{-1}. If cyclohexane is taken as strain-free, the expected ΔH_f for cyclopropane is one-half that for cyclohexane, or −14.75 kcal mol^{-1}. The difference is 27.5 kcal mol^{-1}, and is the strain energy. The strain-free model is frequently derived from Franklin's group equivalent[35], and for common hydrocarbon groups they are in kcal mol^{-1}:

CH_3	−10.12		15.00
CH_2	−4.926		18.88
CH	−1.09		17.83
C	0.80		20.19
			24.57

The strain energies of a variety of cyclopropanes and related compounds are shown in Table 6. In comparing the cycloalkanes, the most surprising observation is that cyclopropane and cyclobutane have essentially the same strain energy despite the much larger bond angle deformation in the three-membered ring. The strain energy per carbon is greater in cyclopropane than in cyclobutane, but not by a large enough amount to correspond to the large difference in angle deformation. The strain energy of cyclobutane results from three factors:

1. the compression of the bond angles from tetrahedral to ~ 90°;
2. the 1,3 repulsion between the cross-ring carbons; and
3. torsional interactions.

The minimum energy geometry is found with a bond angle of 88°, and a torsional angle of 24° (i.e. the ring bent by 35°)[36]. Cyclopropane has two of these interactions (1 and 3), but lacks the cross-ring repulsion. In addition, the C–H bonds in cyclopropane are stronger than those of cyclobutane or larger ring cycloalkanes[37]. Thus, the weaker C–C bonds are in part compensated by stronger C–H bonds. These two factors are in large measure responsible for the similarity in strain energies.

The bicycloalkanes frequently have a strain energy which is the sum of the strain energies of the two rings. Thus, bicyclo[2.1.0]pentane and bicyclo[2.2.0]hexane have strain energies of 52–55 kcal mol^{-1} which is close to twice the strain energies of cyclopropane and cyclobutane. This presumably results from the compensating loss of one destabilizing torsional interaction and an increase in angle strain. There are some cases in which the strain energy is significantly greater than the sum. Bicyclo[1.1.0]butane has 9 kcal mol^{-1} extra strain. Here, the geometry is markedly different than that of cyclopropane. The geometry at the bridgehead is striking. Besides having two CCC angles of only 60°, the bridgehead hydrogen is tilted so that all of the bonds to the carbon are on one side of a plane (i.e. it has an 'inverted' tetrahedral geometry)[38]. The small ring propellanes also have this geometry, and the strain energies are considerably larger than the sum of the strain energies of the component rings. Tetrahedrane also is related to bicyclobutane, and here again the strain energy is much larger than that for four cyclopropane rings. This appears to be a characteristic of cyclopropanes, because the strain energy of cubane is just six times that of cyclobutane.

Another case of increased strain is found with the *trans*-fused bicyclic cyclopropanes. With an eight-membered ring, the *cis*- and *trans*-fused compounds have essentially the

same energy[39]. However, as the ring size is decreased, the strain energy of the *trans*-fused isomer increases markedly, and with a six-membered ring, the *trans* compound is calculated to be destabilized by 42 kcal mol^{-1} compared to the *cis* isomer. These compounds have twist-bent bonds between the bridgehead carbons[40], in which the bonding orbitals are twisted away from each other leading to decreased overlap. Derivatives of *trans*-bicyclo[4.1.0]heptane are known[41], and as might be expected from its strain energy, these compounds undergo relatively facile thermal isomerization to the corresponding *cis* isomers.

In examining the cycloalkenes, one must first recognize that a double bond has considerable inherent strain. For example, the dimerization of ethylene to give cyclobutane is fairly exothermic (-18 kcal mol^{-1}) and if there were a way to readily overcome orbital symmetry restrictions[42], cyclobutane would be a very common reagent. However, in the following, we will take the conventional view that ethylene is unstrained. Then, in comparing cycloalkanes and cycloalkenes it is helpful to define olefinic strain (OS) as the difference in strain between the alkene and the corresponding alkane[43].

Whereas the introduction of a double bond into cyclobutane has only a relatively small effect on the energy (1 and 3 kcal mol^{-1} for one and two trigonal centers, respectively), with cyclopropane, the introduction of one trigonal center increases the strain by 13 kcal mol^{-1}, and two centers increases it by 28 kcal mol^{-1}.

Bicyclobutene is one of the more remarkable of the cyclopropene derivatives, and is predicted to have a bent geometry (48°) and a large barrier to inversion (13 kcal mol^{-1})[44]. The bent geometry is at least in part a means of reducing the angle strain. Bicyclo[2.1.0]pent-1(4)-ene also is calculated to have this geometry. Despite the very large olefinic strain, derivatives of both have been formed and trapped as reaction intermediates[45].

TABLE 6. Heats of formation and strain energies of cycloalkanes and cycloalkenes (kcal mol^{-1})

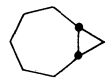
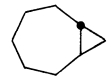
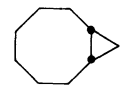
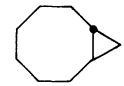
Monocycles

				
ΔH_f	12.73	6.78	−18.44	−29.50
SE	27.5	26.5	6.2	0.0

				
ΔH_f	47.9	29.05	3.29	−8.80
SE	40.9	26.9	6.1	−1.1
OS	13.4	0.4	−0.1	−1.1

				
ΔH_f	66.2	37.45	8.23	−1.08
SE	55.2	28.4	4.1	−0.3
OS	27.7	1.9	−2.1	−0.3

Bicycles and polycycles

						
ΔH_f	51.9	37.7	51	9.09	29.9	15
SE	63.9	54.7	68	31.0	51.8	37
						
ΔH_f	85.0	86	82	61	39.0	136
SE	98	104	105	89	67	140
						
ΔH_f	0.4	42	−3.8	8	−4.96	−4.50
SE	27.2	69	27.9	40	31.7	32.2
						
ΔH_f	145	79.7	136	129	131	
SE	130	67.9	126	120	122	
OS	66	13.2	71	65	67	
						
ΔH_f	62.5	92	88	91		
SE	55.7	87	84	86		
OS	3.9	35	32	55		

SE, strain energy; OS, olefinic strain.

D. Bond Strengths and Force Constants

If the CH bonds of cyclopropane do have increased s character, one would expect them to resemble those of ethylene rather than ethane. With ethylene, it is known that increased s character leads to shorter CH bonds, increased CH bond dissociation energy, and increased CH stretching frequencies. Cyclopropane is compared with propane and ethylene in Table 7. It can be seen that the expectations are met. All of the changes result from the fact that s electrons have a high probability (per unit volume) of being near the nucleus whereas p electrons have a low probability. Therefore, s electrons are bound more tightly than p electrons, leading to shorter and stronger bonds with increasing s character. The relatively high vibrational frequencies for cyclopropyl C–H bonds have been used as a structural tool[49]. However, these bands are frequently weak and may be obscured by other C–H vibrations. The NMR chemical shifts appear to be more generally useful for this purpose.

TABLE 7. Properties of methylene groups

Property	Propane	Cyclopropane	Ethylene
C–H bond length	1.092	1.083	1.085
C–H stretching freq.[46]	2887	3038	3026
C–H bond diss. energy[47]	99	106	109
HCH bond angle	106	114	118
pK_a[48]	51	46	44

Vibrational spectroscopy provides a means of achieving a 'microscopic' examination of groups within molecules. A detailed study of the infrared and Raman spectra of a molecule via a normal coordinate analysis will lead to a set of force constants and interaction constants which are characteristic of the groups within the molecule in question[50]. Similarly, an analysis of the intensities of the infrared bands will lead to the changes in dipole moment which results from distortions of the groups in the molecule[51]. This potential has, however, not been realized until recently because of some problems associated with the analysis of the experimental data. The general solution to the vibrational problem leads to more independent constants than can reasonably be obtained from the observed vibrational frequencies of the parent and several deuterium substituted derivatives[52]. The intensities give the squares of the dipole moment derivatives with respect to the normal coordinates for vibration, and the signs must be recovered in some way in order to make use of them to obtain information concerning the groups in the molecule.

Fortunately, the solution to both of these problems has become available via ab initio molecular orbital calculations. Procedures are now available for calculating the second derivatives of the total energy with respect to the coordinates, which are the force constants[53]. The values are generally about 20% too large, but can readily be scaled to fit the experimental data[54]. Similarly, the calculations may yield the dipole moment derivatives. The values are approximate, but invariably have the correct signs and magnitudes. A number of cycloalkanes and related compounds have been examined in this fashion[55].

In the case of cyclopropane, the vibrational force field and infrared intensities have been examined in some detail both experimentally[56] and via calculation[55]. One of the more interesting observations is that the dipole moment derivatives for the C–H stretching modes are relatively small (corresponding to their low intensities). There is a relationship between the derivatives and the bond dipoles[27]. The low value for cyclopropane is a reflection of the smaller than normal electron population at its hydrogens (Table 3).

The vibrational spectrum of cyclopropene has been examined in detail[52]. Again, the dipole moment derivative for the olefinic C–H stretch was considerably smaller than that for the vinyl C–H stretch, corresponding to the magnitudes of the CH bond dipoles.

The vibrational spectrum of bicyclo[1.1.0]butane has been examined[57], but not with the aid of calculated force constants[58]. Therefore it would be premature to compare the force constants for cyclopropane and bicyclobutane. A complete analysis has been performed for [1.1.1]propellane[34], but again a re-examination of bicyclobutane is needed in order to make meaningful comparisons.

Considerable progress has been made in trying to achieve an understanding of the molecular vibrations of cyclopropane and its derivatives, and it should be possible to bring all of these data together to obtain a detailed picture of how changes in structure affect force constants, interaction constants and dipole moment derivatives.

E. NMR Spectra

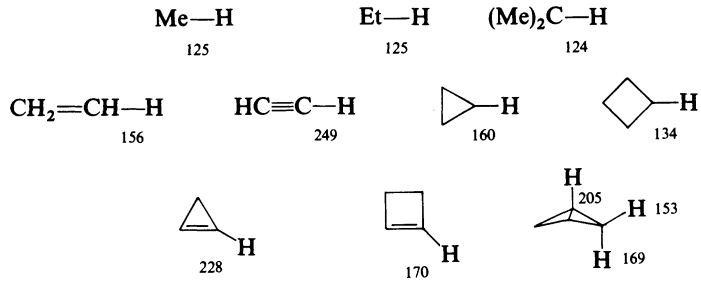
The NMR spectra of cyclopropane derivatives are unique among carbocycles. The ^{1}H-NMR chemical shift of cyclopropane is δ 0.12, considerably upfield from cyclohexane (δ 1.44), whereas the hydrogens of cyclobutane are further downfield (δ 1.96)[59]. The ^{13}C-chemical shift for cyclopropane (-2.9 ppm) also is upfield from that of cyclohexane (27 ppm) or cyclobutane (23 ppm)[60].

The upfield shifts observed with cyclopropanes as well as their larger than normal magnetic susceptibility[61] are reminiscent of benzene. The hydrogens of benzene have a downfield shift, but that is due to the geometry. If they were arranged as in cyclopropane (i.e. above and below the ring and closer to the center) they also would have an upfield shift. The shift in benzene has been attributed to a ring current[62], and so a similar suggestion has been made for cyclopropane[63]. This view has been discussed by several investigators[64], but it seems reasonable to state that the origins of the cyclopropane chemical shifts are still not well understood. The upfield shift is a general property of cyclopropanes, and has been used in structure determination[65].

One difficulty with drawing conclusions from the chemical shifts observed in solution is that they are the averages of the three tensor components. The interaction of a molecule with a magnetic field depends on its orientation, and so it should be represented by three quantities representing the three orthogonal directions. It recently has become possible to measure the tensor components of the ^{13}C-chemical shifts experimentally via solid state NMR spectroscopy[66]. The tensor components for cyclopropane, bicyclo[1.1.0]butane and [1.1.1]propellane are given in Table 8[67]. The isotropic chemical shifts (i.e. the average values observed in solution) at the methylene groups vary widely in this group of compounds (1, 3 and 74 ppm respectively) and an examination of the tensor components shows that the effect is largely due to the component perpendicular to the local C–C–C plane.

The first step in trying to achieve an understanding of the chemical shifts is to be able to reproduce them via calculation. This has been done for the above compounds, and the calculated values also are given in the table[67]. The agreement can only be considered as remarkably good! The ability to calculate these tensor components is a recent development, and it has not as yet been possible to extract a physical model from the calculations. However, it clearly will be only a matter of time before this is developed and one will be able to understand chemical shifts in a much more detailed fashion than is currently possible.

The NMR coupling constants also are of interest. The ^{13}C–H constants vary considerably with bond type, and some typical values are[68]. The coupling constants were



found to be related to the conventional % s character for the CH bonds of methane (25%), ethylene (31%) and acetylene (50%)[69]:

$$J(^{13}\text{C–H}) = 5 \times (\%\ \text{s})$$

TABLE 8. NMR chemical shift tensors

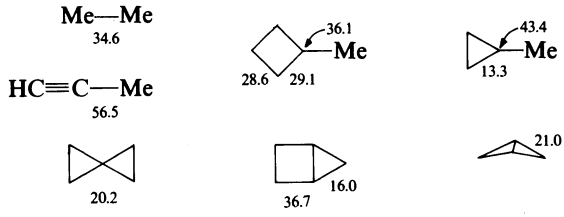
Compound	Tensor	Calc. (ppm)	Expt. (ppm)
Cyclopropane[a]	σ_A	27	22
	σ_B	9	2
	σ_C	−40	−36
	σ_{iso}	−1.3	−4.0
Bicyclobutane CH_2[b]	$\sigma_{A'}$	10	20
	σ_B	38	35
	$\sigma_{C'}$	43	41
	σ_{iso}	30	32
Bicyclobutane CH[c]	$\sigma_{\parallel}$	32	23
	$\sigma_{\perp}$	−24	−19
	$\sigma_{\perp'}$	−26	−21
	σ_{iso}	−6	−6
[1.1.1]Propellane CH_2[a]	σ_A	43	43
	σ_B	53	57
	σ_C	138	138
	σ_{iso}	78	79
[1.1.1]Propellane C[d]	$\sigma_{\parallel}$	30	35
	$\sigma_{\perp}$	−11	−11
	σ_{iso}	3	4

[a] σ_A bisects the HCH angle, σ_B is perpendicular to the HCH plane, and σ_C is perpendicular to the CCC plane.
[b] σ_A, lies along the exo-CH bond, $\sigma_{C'}$ is perpendicular to A′ in the direction away from the endo-CH bond, and σ_B is perpendicular to the HCH plane.
[c] $\sigma_{\parallel}$ is parallel to the central C–C bond, $\sigma_{\perp}$ is perpendicular to the central bond in the H–C–C–H plane, and $\sigma_{\perp'}$ is perpendicular to the H–C–C–H plane.
[c] $\sigma_{\parallel}$ is parallel to the central C–C bond, $\sigma_{\perp}$ is the degenerate component perpendicular to this bond.

It is observed that CH bonds with large s character have large coupling constants. This is expected since the primary mechanism for spin–spin coupling in this case involves electron-spin nuclear-spin interaction. Only the s electrons have a probability of being found at the nucleus, and so only these electrons are able to transmit information concerning nuclear-spin states.

Using this correlation, it is found that the % s character for the CH bonds of cyclopropane is 32%, very close to that of ethylene. The bridgehead CH bond of bicyclobutane would have 41% s character which agrees well with the short CH bond length (Table 3) and relatively high acidity[28]. The methylene CH bonds have normal coupling constants for cyclopropane rings. Cyclopropene has a remarkably large coupling constant for the olefinic protons corresponding to 46% s character, and here again a short bond and high acidity (approaching that of acetylene) is noted[70].

The ^{13}C–^{13}C coupling constants have been examined for many of these compounds[71]. Some typical values are given below. Again, one might expect that the coupling constant would be related to the % s character in the bonds. It is seen that cyclopropane C–C bonds have the smallest coupling constant, and that it increases on going to cyclobutane and to ethane. Similarly, the coupling constant to a methyl group attached to cyclopropane is relatively large, and decreases on going to cyclobutane. The coupling constant to the central carbon in spiropentane is somewhat larger than that for cyclopropane. This carbon is forced by symmetry to use 25% s character in its bonds, and the larger degree of s character results in the increased coupling constant.



In the case of bicyclobutane derivatives, the coupling constants for the central C–C bonds, which should have very little s character[72], ranged from -6 to -17 Hz[73]. The sign of the coupling is reversed from that found with the other bonds. Clearly, the % s character is not the only factor controlling the magnitude of these coupling constants.

F. Interactions with Electron Deficient and Unsaturated Centers

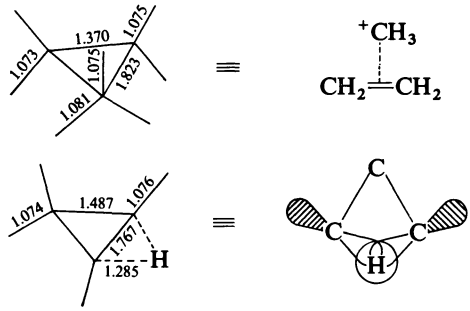
In many ways, cyclopropane behaves in the same fashion as an alkene. This is particularly evident in its interaction with electron deficient centers[1]. Thus, it undergoes a relatively facile reaction with a proton, and its interaction with a cationic center was noted in the introduction.

These cases may conveniently be described as acid–base interactions in which the cyclopropane ring acts as the base (electron donor) and the proton or cationic center acts as the acid (electron acceptor). One of the factors which controls the basicity of a hydrocarbon is the energy of its highest occupied molecular orbital (HOMO)[74]. The HOMO energies (6-31G*) of the cycloalkanes and some alkenes are[75]:

Cyclopropane	-11.35 eV
Cyclobutane	-11.73
Cyclohexane	-11.53
Bicyclobutane	-9.71
Bicyclo[2.1.0]pentane	-10.15
Spiropentane	-10.53
Ethylene	-10.19
Propene	-9.73
cis-2-Butene	-9.26

It can be seen that the HOMO energy of cyclopropane is lower than that of the other cycloalkanes, and that some cyclopropane derivatives have energies similar to those of the alkenes. Another important factor is the polarizability which reflects how easily electron density may be shifted in the presence of an electric field (such as that developed by a proton). Here again, cyclopropanes have significantly greater polarizability than other cycloalkanes[76].

Protonated cyclopropanes have received extensive study, both experimentally and theoretically[77]. Both edge and corner protonated species are possible, and both experiment and theory agree that the energies are very similar. The structures as calculated using the 6-31G* basis set are shown below[76, 78]. The corner protonated species has a very short C_2–C_3 bond, similar to that of an alkene, whereas the other C–C bonds are very long. In this way, it resembles a π complex of a methyl cation with ethylene. The edge protonated species has a longer C–C bond at the site of protonation as might be expected for the formation of a three-center two-electron bond. The structures have been compared with those for the corresponding protonated cyclobutane which have considerably higher energies[76]. The basicity of cyclopropane is considerably larger than that for cyclobutane or



other cycloalkanes. Calculated[78] and experimental values[79] for cyclopropane are compared below, and the calculated value for cyclobutane[76] also is given.

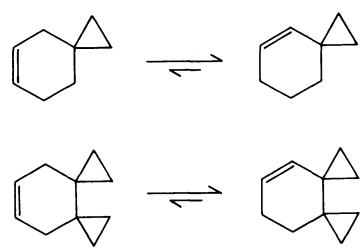
$$CH_3\overset{+}{C}HCH_3 + \triangle \longrightarrow \triangle\!\!-\!\!H^+ + CH_3CH{=}CH_2 \qquad \Delta H_{calc} = 1.9 \text{ kcal mol}^{-1}$$

$$\Delta H_{obs} = 1.0 \text{ kcal mol}^{-1}$$

$$CH_3\overset{+}{C}HCH_3 + \square \longrightarrow \square\!\!-\!\!H^+ + CH_3CH{=}CH_2 \qquad \Delta H_{calc} = 17.9 \text{ kcal mol}^{-1}$$

The interaction with a cationic center, as in the cyclopropylcarbinyl cation, has a similar character. The main difference is that whereas a proton has no stereochemical requirements with respect to its bond to carbon, the cationic center may take different orientations with respect to the cyclopropane ring. Experiment and theory both agree that the preferred geometry is that known as 'bisected' and that rotation of the cationic center by 90° will raise the energy by about 14 kcal mol^{-1} [2]. The preferred conformation is that which allows the p orbital at the cationic center to interact with the in-plane carbon orbitals in the highest occupied MO. This type of interaction also may be seen in the energies of radical cation states of cyclopropane derivatives as determined by photoelectron spectroscopy[80].

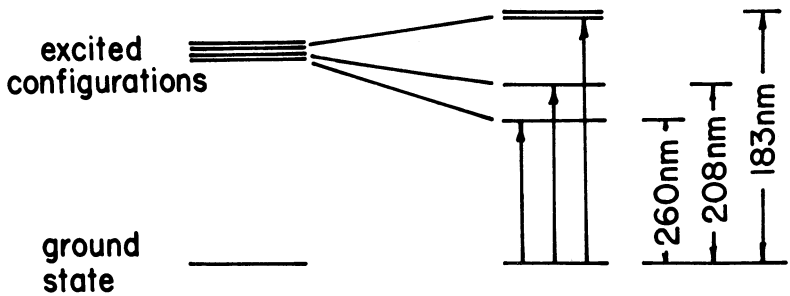
Although the largest effects are seen when the cyclopropane ring is attached to electron deficient centers, significant effects are seen when it is attached to carbon–carbon double bonds or carbonyl groups[1]. A quantitative measure of this effect has been obtained by equilibrating the following double bond isomers. In each case the conjugated isomer was stabilized by about 1 kcal mol^{-1} [81].



G. Electronic Excitation

It is now readily possible to calculate most ground state properties of small organic compounds with satisfactory accuracy via ab initio molecular orbital calculations. It is, unfortunately, much more difficult to examine electronically excited states. With any species, the calculation properly occurs in two stages. First, the conventional molecular orbital calculation is carried out leading to a set of bonding and a set of antibonding molecular orbitals. The Roothan–Hartree–Fock energy (RHF) is obtained using only the bonding orbitals. The second step is to construct a series of configurations by moving one or more of the bonding electrons into antibonding orbitals. The interaction between the ground state configuration and these excited configurations is then calculated (appropriately called configuration interaction) and leads to improved wave functions and energies. In the case of ground states of molecules, the energy gap between bonding and antibonding orbitals is generally rather large, and so the mixing of excited configurations with the ground state is relatively small. As a result, in many cases it is possible to dispense with the second stage of the calculation and simply use the RHF wave functions and energies.

However, with electronically excited states, there are normally many configurations with similar energies. Those having the same symmetry will mix strongly, and the states which result frequently are quite different from those derived from the RHF calculation. Although it may at first appear to have little to do with cyclopropane, the π-electron states of benzene provide a good illustration of the problem. Here, the highest occupied molecular orbitals are degenerate (i.e. both have the same energy) and the lowest unoccupied MOs also are degenerate. Thus, four excited configurations with the same energy may be formed by moving an electron from one of the HOMOs to one of the LUMOs. These four configurations mix strongly and lead to three excited states, two which



are not degenerate, and one which is degenerate. As a result, there are three readily accessible excited π-electron states, and all three are observed in the ultraviolet spectrum. The first two are 'forbidden' and therefore are weak (weakly allowed via coupling with vibrations), whereas the third is allowed and fairly intense.

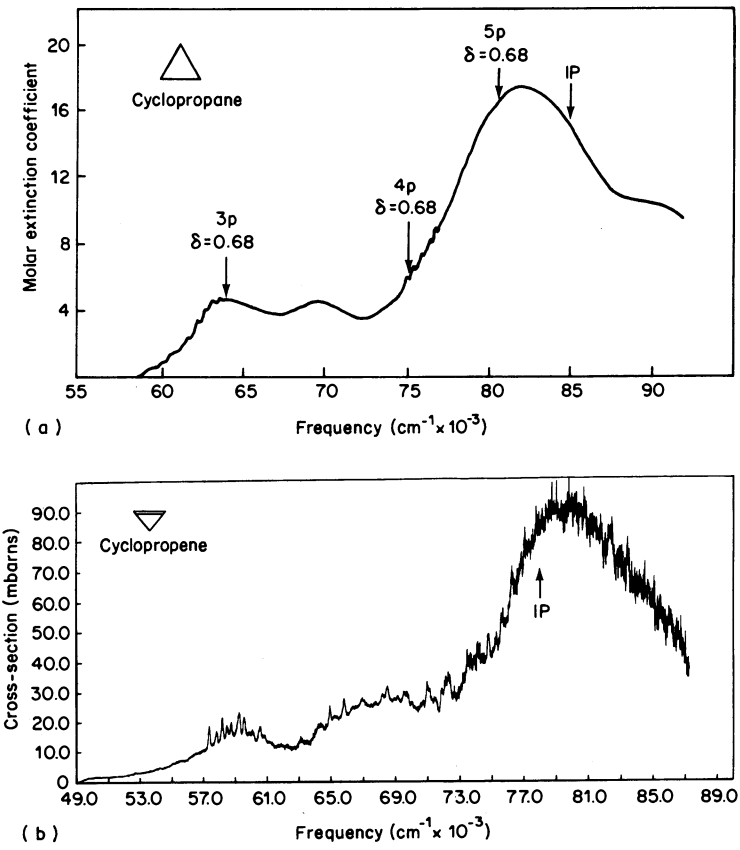
With this introduction, we may examine the electronic spectra of cyclopropane[82], cyclopropene[83] and bicyclobutane[84] (Figure 5). The gap between the occupied and unoccupied orbitals in cyclopropane is greater than that for benzene, and as a result the absorption bands are shifted to higher energies, and into the vacuum ultraviolet (< 200 nm). Cyclopropane is similar to benzene in that it has a degenerate highest occupied molecular orbital. It also has a pair of degenerate unoccupied orbitals, along with two non-degenerate MOs at slightly lower energy. As a result, many relatively low energy singly excited configurations may be developed, and groups of them will interact strongly. Thus, it is not obvious which state will have the lower energy. In addition, some will be forbidden,

will have low intensities and may be difficult to observe. As a further complication, this region is one in which excitation to diffuse states called Rydberg states may also occur, and much of the structure seen in the spectrum of cyclopropane has been attributed to these states. The electronic spectrum of cyclopropane remains poorly understood.

The spectrum of cyclopropene is more interesting. One of the lower energy transitions is $\pi \rightarrow \pi^*$ involving the double bond (58 000 cm^{-1}). Unlike open chain and larger ring cycloalkenes, the double bond is forced to remain in the planar geometry in the excited state. The structure of this transition results from coupling with the C=C stetching vibration. There is a lower energy transition at about 52 000 cm^{-1} which is believed to be a $\sigma \rightarrow \pi^*$ band.

The spectrum of bicyclo[1.1.0]butane has been examined in some detail. The relatively strong band at 53 000 cm^{-1} appears to correspond to the excitation of an electron from the central bond orbital to its antibonding analog. There is a long vibrational progression at somewhat lower energy, and a corresponding progression at higher energy. They appear to arise from two forbidden transitions with the same symmetry. Although the symmetry has been determined, the nature of the states is not at all clear.

The elucidation of the nature of the transitions in these compounds, as well as those of most organic compounds, will depend on the development of sufficiently powerful



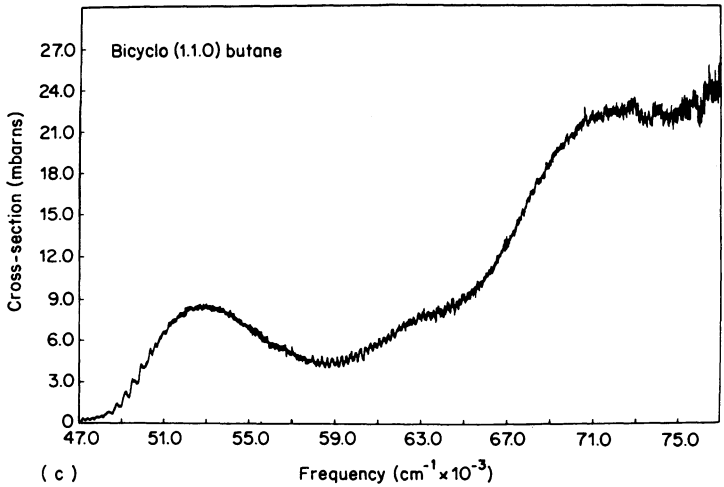


FIGURE 5. Ultraviolet spectra of (a) cyclopropane, (b) cyclopropene and (c) bicyclobutane. The cyclopropane spectrum was taken from Ref. 83 with permission of the American Institute of Physics. The other spectra were taken from the Ph.D. thesis of G. B. Ellison (Yale, 1974)

theoretical tools that will allow the energies, structures and vibrational frequencies of the possible excited states to be calculated, in addition to the band intensities. This is a formidable task, but should yield valuable information about photophysical processes, and ultimately, about photochemical transformations.

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CHAPTER **2**

Chiroptical properties of cyclopropane derivatives

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I. INTRODUCTION

Discussions of chiroptical properties of corresponding compounds in this series of *The Chemistry of Functional Groups* generally refer to the spectral range 589–190 nm, i.e. the emphasis is on optical (molar) rotations $[\Phi]_\lambda^T$ in the transparent region (optical rotatory dispersion, ORD) and rotations $[\Phi]_D^T$ measured at the wavelength of the sodium-D-line ($\lambda = 589$ nm) as well as electronic circular dichroism $\Delta\varepsilon$ (CD) in the near ultraviolet region ($\lambda \geqslant 190$ nm)[1].

According to the general theory[1] the dichroitic absorption $\Delta\varepsilon$ can be deduced from the Cotton effect (CE) of the ORD curve. Here, the ORD amplitude $[a_i]$ for a given electronic transition around the wavelength λ_i is defined as the difference between the rotation values of the peak ($[\Phi]_{\lambda_i}^{max}$) and the trough ($[\Phi]_{\lambda_i}^{min}$) of the ORD curve and one has[1b]:

$$[a_i] = [\Phi]_{\lambda_i}^{max} - [\Phi]_{\lambda_i}^{min} \approx 4028\,|\Delta\varepsilon_i|.$$

With regard to this relationship in this chapter chiroptical properties of three-membered ring compounds in the absorption region will be discussed in terms of $\Delta\varepsilon$ and $[a_i]$, respectively.

The present chapter is largely restricted to cyclopropane derivatives as data on other compounds with a three-membered ring are lacking in the literature. Generally, chiroptical properties intrinsic to the cyclopropane system as well as substituent effects of the cyclopropyl group on chiroptical properties of other types of molecules or chromophores, respectively, will be dealt with.

Current instruments allow CD measurements not only to be performed in the vacuum–ultraviolet (vacuum–UV) region ($\lambda < 190$ nm), but also in the infrared (IR) spectral region. This means that not only chiral absorption effects related to excitations of molecular electronic subsystems are amenable to experimental observations, but also effects involving excitations of the nuclear subsystems of molecules ('vibrational circular dichroism' VCD)[1]. Recently, results of VCD experiments with cyclopropanes were published[2]. Therefore, in the present chapter the discussion of chiroptical properties of cyclopropanes can include vibrational circular dichroism. Hence, the discussions of chiroptical properties of cyclopropanes will cover the spectral range extending from the vacuum–ultraviolet to the infrared region.

Chiroptical properties of chemical compounds are important tools for structural chemistry and stereochemistry because of their extraordinary sensitivity towards configuration and conformation, respectively. In particular, an essential aim of stereochemical research, namely the deductions of absolute configurations of chemical compounds, is achieved mainly via chiroptical properties. For corresponding inferences often qualitative arguments suffice. For instance, the absolute configuration of a compound may be deduced from the sign of a particular CD band resulting from a known electronic transition. Absolute configurations of monocyclic cyclopropanes were mostly deduced from optical rotations, apart from utilizing chemical correlations. For the treatment of molar rotations $[\Phi]_D^T$ of cyclopropanes and also for ORD in the transparent region even a quantitative theory is available[3,4]. As this theory of optical rotations of cyclopropanes is only partly published[5] or documented in non-conventional form[3,4], respectively, pertinent features of this theoretical approach together with relevant results for cyclopropanes will be given more explicitly in this review. The discussion of optical rotations of monocyclic

cyclopropanes will be presented first. Then, electronic CD and, finally, VCD of cyclopropanes will be treated.

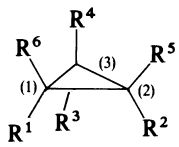
For this review the literature has been surveyed through December 1984.

II. OPTICAL ROTATIONS OF CYCLOPROPANES

A. Semiempirical Descriptions of Optical Rotations of Cyclopropanes by the Triad Theory of Optical Rotations

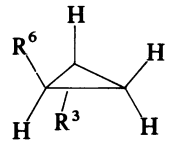
1. General principles

In the literature there exists several theoretical approaches to deal with optical rotations $[\Phi]_D$ of (monocyclic) chiral cyclopropanes **I**[6–9]. In formula **I** R^i corresponds to a substituent R attached to the ligand-site *i*. The enumeration of the skeletal carbon atoms is

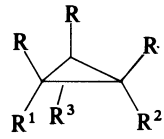


(I)

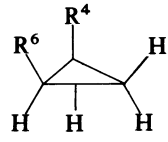
given in parentheses. Except for those presented in Ref. 9 all the calculations of molar rotations of cyclopropanes[6a, 10a, 11–15] were based on Brewster's conformational chirality (dissymmetry) model of optical activity[6]. Apart from numerical disagreements between calculated and observed rotations the above-mentioned theoretical treatments often failed to give even correct signs of the rotations, i.e. wrong absolute configurations were predicted by these methods. Successful calculations were largely restricted to *trans*-disubstituted compounds **II**[6a, 10a, 12, 14, 15]. Furthermore, from a theoretical point of view there is an inherent deficiency in the Brewster method[6] of predicting molar rotations of



(II)



(III)



(IV)

cyclopropanes **I**. According to the Brewster theory zero rotations are predicted for all the chiral cyclopropanes **III** with three identical substituents R in the same plane (R being, for instance, attached to the sites 4, 5, 6). This means, in particular, that within the Brewster scheme for all the *cis*-disubstituted cyclopropanes **IV** zero rotations are predicted, irrespective of the nature of the ligands R^4 and R^6.

All these shortcomings are overcome by the 'triad theory of optical rotations' (TTOR approach)[3,4]. The TTOR approach is a semiempirical theory of optical rotations of (arbitrary) organic compounds in the transparent region ($\lambda \geqslant 300$ nm for cyclopropanes). The theory may be developed in terms of expressions which have a particularly simple mathematical form and which, furthermore, meet the chemists' way of thinking in terms of 'substituent effects'. The mathematical expressions contain only formally defined elements, such as ligand-specific parameters ('rotation parameters') $\lambda(R^i)$, $\nu(R^i)$, etc. These sub-

stituent constants can be determined in the form of numerical values from a restricted set of molar rotations of chiral molecules. With these consequently numerically fixed parameters the rotations of further compounds can be calculated.

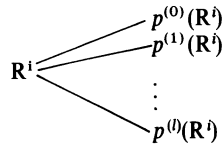
According to the TTOR approach[3] the overall optical rotation Φ_D (at the wavelength of the sodium-D-line) of a statistical ensemble of chiral molecular species in a given geometrical state is a superposition of different rotation terms $\Phi_D^{(i)}$ ($i = 0, 1, 2, \ldots$) (equation 1).

$$\Phi_D = \Phi_D^{(0)} + \Phi_D^{(1)} + \Phi_D^{(2)} + \ldots = \sum_i \Phi_D^{(i)} \tag{1}$$

In equation 1 each term is called a 'source of optical activity' (SOA)[3]. Each SOA describes a particular way of generating optical activity and is built from a number of equivalent 'elements of optical activity' (EOAs)[3]. The elements of optical activity are combined in such a manner that the corresponding SOA has the correct (pseudoscalar) transformation property to describe optical rotations.

An element of optical activity of a chiral object is the most fundamental (elementary!) unit which, by virtue of its transformation property, can induce optical activity. The EOA will be characterized by certain scalar parameters.

On the molecular level the TTOR approach assumes that three different types of EOA (a triad!) suffice to explain the generation of optical rotations of organic compounds. First, an EOA may transform like a regular geometrical body of point-symmetry G with a singular point. It, hence, has a center of chirality[1c]. Second, an EOA may transform like a helix. And, finally, it may transform like a polar plane (the corresponding molecular system having a plane of chirality)[1c]. It may be, of course, that a given compound does not exhibit all the above three types of EOA. For instance, a given compound may have only EOAs of the corresponding type, such as two different kinds of helices. As a consequence, in the TTOR-approach each ligand R of a molecule is associated with several parameters $p^{(k)}(R)$ ($k = 0, 1, 2, \ldots$) which characterize the effect of a particular group within a definite EOA.



The fundamental methodological problems facing the TTOR-approach which emerge from the preceding discussions are to determine

(*a*) which of the several (conceivable) elements of optical activity are associated with a given type of compound,
(*b*) how many of them are to be included into a numerical treatment in order to obtain a reasonable good quantitative description of optical rotations, and
(*c*) what are the analytical forms of the functions $\Phi_D^{(i)}$.

Using geometrical point-models for molecules the stereochemistry of organic compounds is described on the lowest level in terms of constitution and configuration, i.e. the sequential arrangements of atoms in the molecules regardless of their directions in space (constitution) and the relative positions of the atoms and/or groups in space (configuration). The next level of describing the stereochemistry of organic compounds takes into consideration the actual disposition of the atoms in space in terms of bond distances, bond angles, dihedral angles etc. Referring only to the configurational level of describing optically active cyclopropanes **I** one easily finds three different elements of optical activity (Figure 1)[3]. These EOAs may be symbolized by a prism of symmetry D_{3h}, an irregular C_{2v}-tetrahedron and a four-point helix.

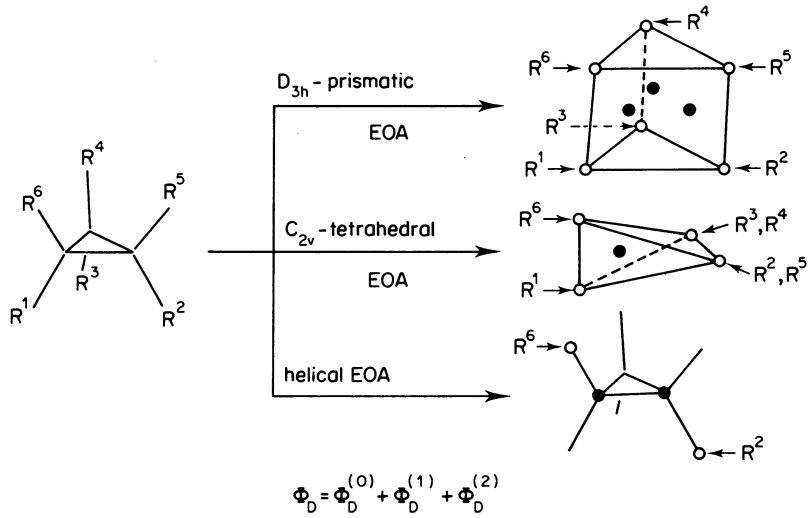


FIGURE 1. Elements of optical activity (EOA) for the description of optical rotations of cyclopropanes referring to the configurational level of representing molecules

In the TTOR approach the six RCCR′-type helices are combined to give the helical source of optical activity of cyclopropanes ($\phi_D^{(0)}$). The three C_{2v}-tetrahedral EOAs generate the tetrahedral SOA ($\phi_D^{(1)}$). The three C_{2v}-tetrahedral EOAs may be related to the three skeletal atoms of the cyclopropanes **I**. Hence, the generation of optical rotations of cyclopropanes **I** by the C_{2v}-tetrahedral EOAs may be compared with the induction of optical rotations of methanes with an asymmetric carbon atom[3, 5]. The contributions $\Phi_D^{(0)}$ and $\Phi_D^{(1)}$ results from the optical activity of particular subsystems of the cyclopropane molecules. On the other hand, the last contribution, $\Phi_D^{(2)}$, originates with the chirality of the whole molecular species represented by the cyclopropane D_{3h}-arrangement of the ligand-sites (Figure 1). This means that in this last case the SOA $\Phi_D^{(2)}$ is identical with the corresponding EOA (the SOA is said to be one-dimensional)[3].

In Ref. 4 it has been shown that for a numerically adequate description of optical rotations of cyclopropanes **I** in the 'standard' solvent chloroform a restriction to the terms $\Phi_D^{(0)}$ and $\Phi_D^{(1)}$ suffices, i.e. the optical rotations of **I** can be described in terms of helix optical activity and atomic asymmetry (equation 2).

$$\begin{aligned}\Phi_D(\mathbf{I}) &= \Phi_D(R^1, R^2, R^3, R^4, R^5, R^6) \\ &= \Phi_D^{(0)}(R^1, \ldots R^6) + \Phi_D^{(1)}(R^1, \ldots R^6)\end{aligned} \tag{2}$$

The helix contribution $\Phi_D^{(0)}$ is given by equation 3[4]. In equation 3 $\lambda(R^i)$ is a ligand-specific parameter which characterizes the optical rotation of a RCCR′-helix of cyclopropanes **I**.

$$\begin{aligned}\Phi_D^{(0)}(R^1, \ldots R^6) = -[&(\lambda(R^1) - \lambda(R^2))(\lambda(R^6) - \lambda(R^4)) \\ &- (\lambda(R^1) - \lambda(R^3))(\lambda(R^6) - \lambda(R^5))]\end{aligned} \tag{3}$$

The helix contribution $\Phi_D^{(0)}$ has the specific property that it vanishes for all the cyclopropanes **III** which have three identical ligands $R = R^4 = R^5 = R^6$ in the same plane, irrespective of the nature of the ligands R^i (equation 4). This is comparable to the situation

in the Brewster theory of optical rotations of cyclopropanes[6].

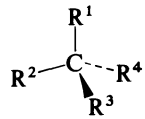
$$\Phi_D^{(0)}(R^1, R^2, R^3, R, R, R) = 0 \tag{4}$$

Cyclopropanes of types **III** or **IV**, respectively, therefore, provide situations where the optical activity of cyclopropanes is solely due to the atomic asymmetry term $\Phi_D^{(1)}$. The total contribution from all the three asymmetric (cyclopropane) carbon atoms, i.e. the C_{2v}-tetrahedral SOA $\Phi_D^{(1)}$, is given by equations 5a and 5b[4].

$$\Phi_D^{(1)}(R^1, \ldots R^6) = \varphi_{D,(1)}^{(1)} + \varphi_{D,(2)}^{(1)} + \varphi_{D,(3)}^{(1)} \tag{5a}$$

$$\begin{aligned}\Phi_D^{(1)}(R^1, \ldots R^6) = {} & \tilde{\alpha}(R^1)\cdot\tilde{\alpha}(R^6)\cdot(\mu(R^6)-\mu(R^1)) \\ & \times [\nu(R^2)+\nu(R^5)-(\nu(R^3)+\nu(R^4))] \\ & + \tilde{\alpha}(R^3)\cdot\tilde{\alpha}(R^4)\cdot(\mu(R^4)-\mu(R^3)) \\ & \times [\nu(R^1)+\nu(R^6)-(\nu(R^2)+\nu(R^5))] \\ & + \tilde{\alpha}(R^2)\cdot\tilde{\alpha}(R^5)\cdot(\mu(R^5)-\mu(R^2)) \\ & \times [\nu(R^3)+\nu(R^4)-(\nu(R^1)+\nu(R^6))]\end{aligned} \tag{5b}$$

In equation 5 the parameters $\tilde{\alpha}(R)$ correspond to the (isotropic) group polarizabilities as given in Refs 4 and 16 (and partly in Ref. 5). The parameters $\mu(R)$ and $\nu(R)$ are further rotation parameters associated with the groups directly attached to a particular skeletal carbon atom and with the remote groups, respectively. The parameters $\tilde{\alpha}(R)$ and $\mu(R)$ are exactly those which are used to calculate the optical rotations of methane derivatives **V** according to equation 6[5, 16].



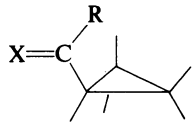
(V)

$$\begin{aligned}\Phi_D(R^1, R^2, R^3, R^4) = {} & \tilde{\alpha}(R^1)\cdot\tilde{\alpha}(R^2)\cdot\tilde{\alpha}(R^3)\cdot\tilde{\alpha}(R^4) \\ & \times [\mu(R^1)-\mu(R^2)][\mu(R^1)-\mu(R^3)][\mu(R^1)-\mu(R^4)] \\ & \times [\mu(R^2)-\mu(R^3)][\mu(R^2)-\mu(R^4)][\mu(R^3)-\mu(R^4)]\end{aligned} \tag{6}$$

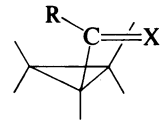
Hence, in equation 5 the expression $\tilde{\alpha}(R^1)\cdot\tilde{\alpha}(R^6)\cdot(\mu(R^6)-\mu(R^1))$ for the geminal groups R^1 and R^6, for instance, may be viewed as that part of the rotation contribution of an asymmetric carbon atom which can be transferred from acyclic compounds **V** to the cyclic compounds **I**.

The restriction of the theoretical treatment of optical rotations of cyclopropanes **I** to the basis of equations 2, 3 and 5 has several implications with regard to the descriptions of molecules on the conformational level. A discussion of some special cases shall demonstrate that the success of equation 2 does not mean that for the theoretical treatment of optical rotations only the configurational level for representing molecules is relevant. On the contrary, an adequate description of optical rotations of organic compounds must take the various conformations of the compounds and the conformer equilibria explicitly into account[3, 16]. The very point is that, due to favorable conformational equilibria, often rotation contributions from conformational effects are small or cancel (to a large extent).

For instance, in solutions substituted cyclopropanes with locally planar groups, such as the acetyl (MeC=O) or vinyl (H_2C=CH) groups, may exist as equilibria of several conformers. One can find 'bisected' (**VI**) 'perpendicular' (**VII**) or 'intermediate' (gauche) conformations[17-21]. In these conformations, furthermore, s-*trans* and s-*cis* arrangements

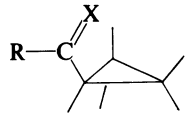


(**VI**)



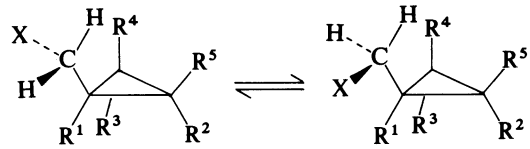
(**VII**)

of the relevant groups may exist, such as **VI** and **VIII**. In principle, the rotation parameters should be different for the various orientations of such groups. In the bisected



(**VIII**)

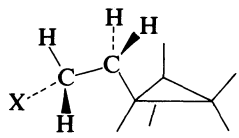
conformation one should have, for instance, for the s-*trans* (*t*) and s-*cis* (*c*) forms $\lambda(t - RC{=}X) \neq \lambda(c - RC{=}X)$. The success of using fixed ('averaged') parameters λ, $\tilde{\alpha}$, μ, or ν for locally planar substituents means that the ratio between the various arrangements of RC=X in a cyclopropane molecule is little affected by the other groups of the molecule. On the other hand, it may also be that the parameter values for the various arrangements (e.g. $\lambda(t - RC{=}X)$, $\lambda(c - RC{=}X)$ etc.) differ only little. Referring to the conformational level of describing molecules it may be that for cyclopropanes with certain groups in addition to equation 2 further rotation contributions (in the sense of equation 1) must be taken into account. For instance, in cyclopropanes with CH_2X groups (X = Cl, Br, I, CN, OMe etc.) helical EOAs will exist involving the $XCC(1)R^1$ and $HCC(1)R^1$ moieties. However, as long as equimolar (or almost equimolar) mixtures of the preferred (gauche)[17] conformations **IXa** and **IXb** are present, the rotation contributions from these particular helices will cancel (if $X/R^4,R^3$ and $X/R^5,R^2$ interactions can be neglected). Cyclopropanes **X** with



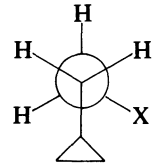
(**IXa**) (**IXb**)

$(CH_2)_2X$ groups, on the other hand, may provide rotation contributions which are related to the ethane-type helical optical activity of alkyl chains[3, 6, 16] ('side-chain optical activity'). If in solution the conformers **Xa** and **Xb** (which are enantiomers for $R^4 = R^3$ and $R^2 = R^5$) are found in equal amount, the overall side-chain optical activity will add to a zero (or almost zero) rotation.

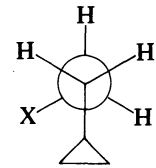
The résumé of the above outline is that the success of equations 2, 3 and 5 is often due to the fact that optical rotation contributions from substituents attached to the cyclopropane skeleton can be neglected as a result of cancelling effects. Hence, a discussion of



(X)



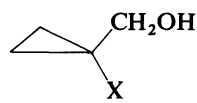
(Xa)



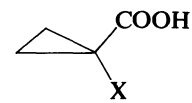
(Xb)

disagreement between calculated and observed optical rotations will first tackle the question whether side-chain optical activity is no longer negligible for the particular sample.

On the other hand, some special situations can be anticipated where the TTOR approach to optical rotations of cyclopropanes based on equations 2, 3 and 5 will fail. This will probably be the case, if hydrogen bonding between geminal or *cis*-vicinal ligands occurs and cyclic structures are formed. Formation of cyclic structures has a decisive influence on optical rotations[7, 16]. In terms of the TTOR approach these cyclic structures bring forth additional rotation contributions (in the sense of equation 1). Cyclopropanes whose optical rotations probably cannot be treated with the TTOR approach will have, for instance, a hydrogen bond acceptor group, such as F, Cl, Br, MeO and also Ph, and a substituent bearing a hydroxy group, such as OH, CH_2OH, COOH, $(CH_2)_2OH$ etc. Such cyclopropanes will be of the types **XI** and **XII** or cyclopropyl amino acids (X = NH_2 in **XII**) with hydrogen bonds between geminal groups.



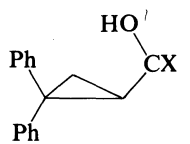
(XI)



(XII)

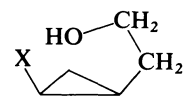
X = F,Cl,Br,OMe,Ph

Cis-vicinal hydrogen bonds with consequences for optical rotations may occur, for instance, in 1,1-diphenylcyclopropanes **XIII** or 2-cyclopropylethanols **XIV**.



X = O,H_2

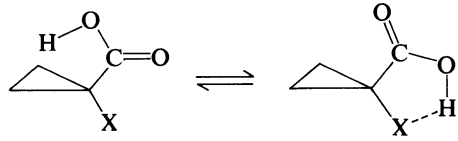
(XIII)



X = F,Cl,OMe,Ph

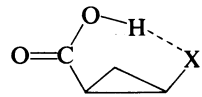
(XIV)

The effect of an intramolecular hydrogen bond on the optical rotation may not only be the formation of a cyclic structure. The hydrogen bond may also enforce a particular conformation of the group involved in the hydrogen bonding. For instance, in (geminal) 1-halogenocyclopropane-1-carboxylic acids it may be that only the hydrogen bonded species with an s-*cis* conformation (**XVb**) of the carboxy group is present, whereas for other compounds there is an equilibrium of the s-*cis* and s-*trans* forms. Actually, in **XVa** the OH hydrogen may also form a hydrogen bond with the electron rich 'edge' of the cyclopropyl ring[17]. This means that the equilibrium **XVa** $\rightleftharpoons$ **XVb** represents an equilibrium between two intramolecularly differently bonded species.



(XVa) (XVb)

On the other hand, it is obvious that a *cis*-vicinal hydrogen bond, as in 2-halogenocyclopropane-1-carboxylic acids **XVI**, will enforce an s-*trans* arrangement of the carboxy group. Using the hydrogen bond acceptor chloroform as the standard solvent for

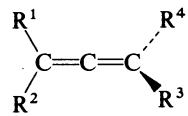


(XVI)

optical rotation measurements in the above types of cyclopropanes **XI–XVI** intramolecular and intermolecular hydrogen bonding (with the solvent molecules) will compete and the cyclic structures will be largely destroyed. Therefore, one can expect that in the standard solvent (or alcohols as the solvents) the optical rotations can be predicted with acceptable accuracy on the basis of equations 2, 3 and 5 also for cyclopropanes of the above types **XI–XVI**.

2. *Parameters for the calculations of molar rotations*

The parameters which are necessary to calculate molar rotations $[\Phi]_D$ of cyclopropanes **I** (in chloroform, methanol, or ethanol) are given in Table 1. If one differentiates substituents bonded via a carbon atom to the cyclopropane skeleton and substituents bonded via a heteroatom, the λ-parameters (which describe helix optical activity) exhibit two correlations with the parameters $\lambda_A(R)$ which are used to calculate the molar rotations of allenes **XVII**[22] (Figure 2). This means that the helix contribution $\Phi_D^{(0)}$ (equation 3) to the



(XVII)

molar rotations of cyclopropanes **I** (generated by R^iCCR^j helices) is similar to that of compounds with an unsaturated molecular skeleton. In the allenes **XVII** helix optical activity is induced by $R^iC{=}C{=}CR^j$ helices[22]. The above observation of the relationship between rotation parameters for cyclopropanes and allenes is in line with attributing 'double bond' character to the cyclopropane CC bonds[17, 20, 23, 24]. In particular, the chemical and physical properties of the cyclopropane moiety have been recognized as being generally similar to those of a C=C double bond[20]. This analogy is generally valuable also for qualitative discussions of chiroptical properties of cyclopropanes.

More insights into the substituent effects which are responsible for the generation of helix optical rotations of cyclopropanes **I** can be obtained through a dual substituent parameter (DSP) approach[25]. Referring to the polar substituent constant σ_I[25] (which

TABLE 1. Parameters for the calculations of molar rotations of cyclopropanes[4]

R	λ (R)	ν (R)	$\tilde{\alpha}$ (R) (Å^3)	μ (R)
H	0.0	0.0	0.664	0.6640
Me	−8.5	−9.16	2.509	2.1439
Et	−14.3	−15.93	3.125	3.4472
n-Pr	−15.0	−16.5	3.125	3.4881
i-Pr	−18.0	−20.0	3.745	2.2409
t-Bu	−19.2	−21.0	4.365	2.2096
CH_2OH	−10.9	−12.17	2.798	2.1789
CH_2CH_2OH	−14.3	−20.50	3.125	3.4881
CH_2CH_2Br	−14.3	−15.93	3.125	3.4881
CH_2COOMe	−10.9	−12.17	3.125	2.1813
Ph	−33.0	−5.64	2.767	3.5156[a]
$HC{=}CH_2$	−28.0	−30.75	3.086	3.5355
$HC{=}CMe_2$	−21.2	−30.75	3.086	3.5355
$MeC{=}CH_2$	−21.2	−30.75	3.766	3.5355
COOH	−19.2	−11.00	2.729	3.5610
COOMe	−21.5	−19.69	2.776	3.5720
COOM[b]	−23.0	−12.0	2.776	3.5100
CHO	−28.0	−30.0	2.532	3.5594
COMe	−28.0	−30.0	3.152	3.5594
COPh	−28.0	−30.0	3.152	3.5594
CN	−21.7	−20.88	2.420	3.6229
NC	−25.5	−40.0	3.176	3.5530
NH_2	−17.0	−73.82	2.013	2.1211
NH_3X[c]	−22.1	−45.0	2.567	2.1727
MeO	−10.0	−65.0	1.888	1.9578
F	−8.0	−80.0	0.578	1.6564
Cl	−17.0	−26.0	2.573	3.5574
Br	−24.0	−44.0	3.722	3.5537
I	−32.8	−62.0	5.788	3.5486

[a] For phenylcyclopropanes in MeOH, EtOH, or $CHCl_3$ as the solvent.
[b] M = Na^+, K^+, NH_4^+.
[c] X = Cl, Br.

reflects the effect of the group's dipole moment) and the group polarizability $\tilde{\alpha}$(R) the λ(R)-parameters may be described by equation 7 (using the substituents H, Me, F, Cl, I, COOMe, MeO as the basis set)[4].

$$\lambda(\mathrm{R}) = 3.38 - 19.20\,\sigma_\mathrm{I} - 5.19\,\tilde{\alpha}(\mathrm{R}) \tag{7}$$

Equation 7 shows that in cyclopropanes helix optical activity is not only induced by the groups' polarizabilities, but to a large extent also by the groups' polarities ($4 \cdot \sigma_\mathrm{I}$ is a rough measure for the group dipole moments).

For the ν(R)-parameters no correlation involving the group polarizability $\tilde{\alpha}$(R) exists[4]. However, it was found[4] that ν(R) depends on σ_I and the resonance substituent constants $\sigma_\mathrm{R}^{\mathrm{BA}}$[25] according to equation 8, both substituent effects having significant weights for ν(R).

$$\nu(\mathrm{R}) = -6.04 - 52.10\,\sigma_\mathrm{I} + 72.84\,\sigma_\mathrm{R}^{\mathrm{BA}} \tag{8}$$

The other parameter, μ(R), which describes the C_{2v}-tetrahedral contribution $\Phi_\mathrm{D}^{(1)}$ to the optical rotations of cyclopropanes **I** is related to the 'distance' x_{CR} between the asymmetric carbon atom and the center of the polarizability in the C–R unit[16].

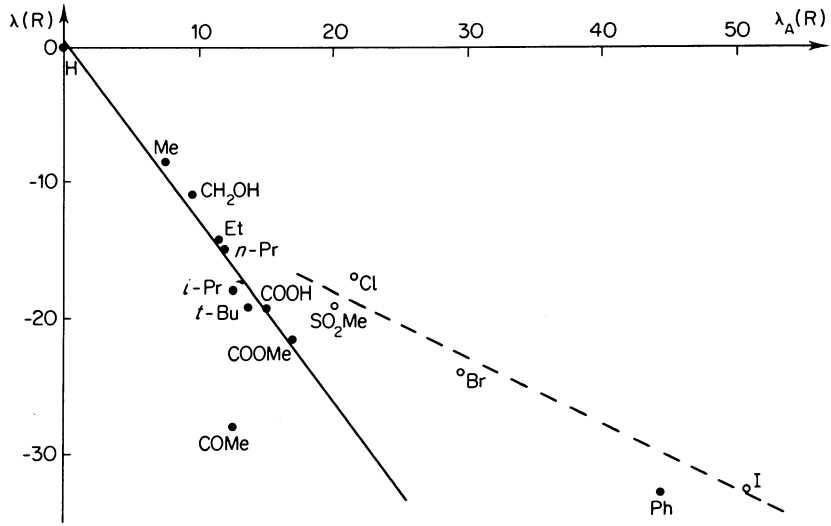


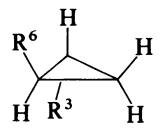
FIGURE 2. Correlations between the parameters to calculate helical optical rotations of allenes, $\lambda_A(R)$, and cyclopropanes, $\lambda(R)$

3. *Calculations of molar rotations of cyclopropanes*

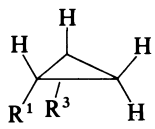
a. Cyclopropanes with two substituents

In Ref. 4 comparisons between theoretical and experimental molar rotations of a large number of cyclopropanes are presented. In the following subsections an arbitrary selection from these results will be presented. The predictions of optical rotations simultaneously provide determinations of absolute configurations.

At first compounds with only two substituents shall be considered. For the *trans*-disubstituted cyclopropanes **II** equations 2, 3 and 5 take the form of equation 9.



(II)



(IV′)

$$\Phi_D(\mathbf{II}) = \Phi_D^{(0)}(\mathbf{II}) + \Phi_D^{(1)}(\mathbf{II}) \tag{9a}$$

$$\Phi_D(\mathbf{II}) = -\lambda(R^3)\cdot\lambda(R^6) - \tilde{\alpha}(R^6)\cdot\tilde{\alpha}(H)\cdot(\mu(R^6) - \mu(H))\cdot\nu(R^3) - \tilde{\alpha}(R^3)\cdot\tilde{\alpha}(H)\cdot(\mu(R^3) - \mu(H))\cdot\nu(R^6) \tag{9b}$$

For the *cis*-disubstituted cyclopropanes **IV′** the optical rotation results from only the C_{2v}-tetrahedral SOA $\Phi_D^{(1)}$, i.e. from atomic asymmetry according to equation 10.

$$\Phi_D(\mathbf{IV}') = \tilde{\alpha}(R^1)\cdot\tilde{\alpha}(H)\cdot(\mu(R^1) - \mu(H))\cdot\nu(R^3) - \tilde{\alpha}(R^3)\cdot\tilde{\alpha}(H)\cdot(\mu(R^3) - \mu(H))\cdot\nu(R^1) \tag{10}$$

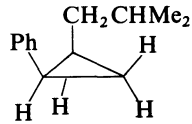
Comparisons between calculated (Φ_D) and observed ($[\Phi]_D$) molar rotations of disubstituted cyclopropanes are presented in Table 2. In the ninth column of Table 2 the *z*-numbers which are used as measures of the quality of the fit between $[\Phi]_D$ and Φ_D are given. The accuracy *z* is defined according to equation 11[3] and incorporates the deviations

$$\Delta = [\Phi]_D - \Phi_D.$$

$$z = 100 \times \frac{|\Delta|}{\max\{|[\Phi]_D|, 10\}} \tag{11}$$

The *z*-number corresponds to the relative error (in percent), if the absolute magnitude of the experimental rotation $[\Phi]_D$ exceeds 10°. For $|[\Phi]_D| \leqslant 10°$, *z* corresponds to the tenfold absolute error (in degrees). In this way, the accuracy of the theoretical treatment can be adequately judged for large, but also small optical rotations of cyclopropanes. The molar rotations of the compounds in Table 2 extend over 1000° (**8** vs. **19**). In general, agreements between theoretical and experimental rotations are satisfying ($z < 40$) giving credit to the TTOR approach in its truncated form. In some few cases (**21**, **27**, **28**, **30**, **31**) larger deviations ($z > 50$) are observed. In one case, *cis*-2-methylcyclopropane carboxylic acid (**14**), even a wrong sign for the rotation is predicted. In Ref. 4 it has been suggested that for the *cis*-acid **14** the discrepancy is probably due to a solvent effect (steric hindrance of solvation) and/or a conformational effect of the COOH group as a result of an interaction with the *cis*-vicinal methyl group.

The data in Table 2 show that the rotations of *cis*-substituted cyclopropanes are often considerably smaller than those of the corresponding *trans* compounds. If the cyclopropane bears a phenyl ring the relationship between the magnitude of the rotations of *cis* and *trans* compounds is not obvious. For instance, the rotation of the *cis*-phenylcyclopropane carboxylic acid **23** is small compared with the rotation of the *trans* compound **22**; and also the rotation of the *cis*-phenylcyclopropane **32** is rather small[31]. On



$[\Phi]_D + 33.3°$

(32)

the other hand, the rotations of the *cis*-phenylcyclopropanes **30** and **31** are very close to those of the corresponding *trans* compounds **20** and **21**. With regard to the mechanism of the generation of the optical rotations of *trans*-disubstituted cyclopropanes the results of Table 2 show that for molecules with alkyl or σ-inductive groups the helix contribution $\Phi_D^{(0)}$ and the C_{2v}-tetrahedral SOA $\Phi_D^{(1)}$ are of comparable magnitude. Both these terms have different signs and, hence, add to rather small overall rotations ($\Phi_D < 50°$).

If a mesomeric group is attached to the cyclopropane skeleton the helix contribution $\Phi_D^{(0)}$ is considerably larger than the atomic asymmetry term $\Phi_D^{(1)}$. The resulting rotation Φ_D mostly exceeds 100°. For phenylcyclopropanes with mesomeric π-acceptors (COOH, COOMe, Ph) or a weak σ-donor (Me) *trans* to the phenyl ring the helix term dominates the overall rotation. For *trans*-phenylcyclopropanes with medium to strong π-donors (NH_2, Cl, I) the helix contribution remains dominant, but the atomic asymmetry term $\Phi_D^{(1)}$ becomes very large ($|\Phi_D^{(1)}| > 150°$).

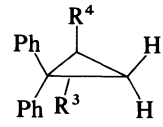
(b) Cyclopropanes with more than two substituents

The largest class of optically active complex cyclopropanes (with more than two substituents) is represented by the 1,1-diphenylcyclopropanes **XVIII**.

TABLE 2. Calculated (equations 9, 10)[a] and observed molar rotations of disubstituted[b] cyclopropanes[4]

Compound	R^1	R^6	R^3	$\Phi_D^{(0)}$ (deg)	$\Phi_D^{(1)}$ (deg)	Φ_D (deg)	$[\Phi]_D$ (deg)	z	Ref.
1	H	Me	Me	−72.25	+45.17	−27.03	−32.26 (diglyme)	16.2	13
2	H	*n*-Pr	*n*-Pr	−225.00	+193.38	−31.62	−28.53 (neat)	10.8	26
3	H	Et	Me	−121.55	+88.37	−33.18	−29.96 (C_6H_{14})	10.8	10a
4	Et	H	Me	—	−13.62	−13.62	−13.63 (C_7H_{16})	0.0	10a
5	H	CH_2COOMe	Me	−92.65	+58.84	−33.81	−33.58 ($CHCl_3$)	0.7	10a
6	CH_2COOMe	H	Me	—	+1.16	+1.16	+1.17 ($CHCl_3$)	1.0	10a
7	H	CH_2CH_2OH	Me	−121.55	+100.35	−21.20	−34.96 (MeOH)	39.4	10a
8	CH_2CH_2OH	H	Me	—	+0.73	+0.73	+0.22 ($CHCl_3$)	5.1	10a
9	H	CH_2OH	CH_2OH	−118.81	+68.50	−50.31	−62.82 (EtOH)	19.9	13
10	H	COOH	COOH	−368.64	+115.49	−253.15	−307.71 (EtOH)	17.7	2, 13
11	H	COOMe	COOMe	−462.25	+211.09	−251.16	353.2 (MeOH)[d], −366.8[c]	28.9	2, 13
12	H	CN	CN	−650.25	+198.55	−451.70	−350.9 ($CDCl_3$)	28.7	2
13	H	COOH	Me	−163.20	+75.22	−87.98	−77.49 (EtOH)	13.5	10a, 12
14	COOH	H	Me	—	−20.97	−20.97	+28.63 (EtOH)	173.2	10a, 12
15	H	COMe	Me	−238.00	+129.47	−108.53	−135.20 (dioxane)	19.7	27
16	COMe	H	Me	—	+18.45	+18.45	+41.96 (dioxane)	56.0	27
17	H	CN	Me	−184.45	+95.03	−89.49	−85.18 ($CHCl_3$)	5.1	10a
18	CN	H	Me	—	+7.93	+7.93	+8.27 ($CHCl_3$)	3.4	10a
19	H	Ph	Ph	−1089.00	+59.10	−1029.90	−1029.7 (EtOH)	0.0	15
20	H	Ph	Me	−280.50	+61.90	−218.60	−148.7 ($CHCl_3$)	47.0	12
21	H	Ph	CH_2OH	−359.70	+79.63	−280.07	−134.6 (EtOH)	108.1	12
22	H	Ph	COOH	−633.60	+87.24	−546.36	−505.6 (EtOH)	8.1	13
23	Ph	H	COOH	—	−28.02	−28.02	−55.99 ($CHCl_3$)	50.0	28
24	H	Ph	COOMe	−709.50	+133.39	−576.11	−590.5 (EtOH)	2.4	12, 28
25	Ph	H	COOMe	—	−72.93	−72.93	−89.87 (EtOH)	18.9	28
26	H	Ph	NH_2	−561.00	+397.74	−163.26	−156.5 (dioxane)	4.3	29
27	H	Ph	NH_3Cl	−729.30	+250.26	−479.04	−128.1 (H_2O)	274.0	30
28	H	Ph	Cl	−561.00	+164.10	−396.90	−229.0 ($CHCl_3$)	73.3	15a
29	H	Ph	I	−1082.40	+387.36	−695.04	−565.2 ($CHCl_3$)	23.0	15a
30	Ph	H	CH_2OH	—	− 47.89	−47.89	−133.7 ($CHCl_3$)[e]	64.2	15a
31	Ph	H	Me	—	−34.08	−34.08	−97.98 ($CHCl_3$)[e]	65.2	15a

[a] In $CHCl_3$, EtOH, or MeOH.
[b] $R^2 = R^4 = R^5 = H$.
[c] $[\Phi]_{578}$.
[d] estimated according to $[\Phi]_D \approx (\lambda/589)^2 \cdot [\Phi]_\lambda$.
[e] Synthesized from **23** with $[\alpha]_D$ −15.0° ($CHCl_3$) (o.p. 43.45%).



(XVIII)

All these compounds **XVIII** are made available by the monumental work of Walborsky[11,13,32–40]. For the 1,1-diphenylcyclopropanes **XVIII** equations 2, 3 and 5 take the form of equation 12.

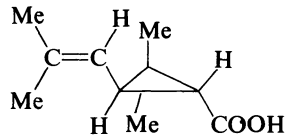
$$\Phi_D(\mathbf{XVIII}) = \Phi_D^{(0)}(\mathbf{XVIII}) + \Phi_D^{(1)}(\mathbf{XVIII}) \tag{12a}$$

$$\Phi_D(\mathbf{XVIII}) = -\lambda(\mathrm{Ph}) \cdot [\lambda(R^3) - \lambda(R^4)] + 2 \cdot \tilde{\alpha}(R^3) \cdot \tilde{\alpha}(R^4) \cdot (\mu(R^4) - \mu(R^3)) \cdot \nu(\mathrm{Ph}) \tag{12b}$$

Theoretical and experimental molar rotations of 1,1-diphenylcyclopropanes are summarized in Table 3.

Only the methoxy- and chloro-compounds (**38**, **39**) exhibit large deviations between calculated and observed rotations. In general, the 1,1-diphenylcyclopropanes **XVIII** have rather large optical rotations ($|[\Phi]_D| > 90°$). Inspection of Table 3 reveals that the molar rotations of **XVIII** are almost entirely due to helix optical activity ($|\Phi_D^{(0)}| \gg |\Phi_D^{(1)}|$). This is in contrast to an earlier assumption[42] which has attributed optical rotations of **XVIII** to atomic asymmetry. Further comparisons between calculated and observed optical rotations of complex cyclopropanes **I** are presented in Table 4.

For the phenylcyclopropanes **44–52** agreements between Φ_D and $[\Phi]_D$ are fair to good. As usually observed with phenylcyclopropanes (Tables 2, 3) the overall rotations of **44–52** are governed by helix optical activity ($\Phi_D^{(0)}$). Especially for the geminal dihalogeno compounds **44** and **45** the (theoretical) atomic asymmetry terms are very large ($|\Phi_D^{(1)}| > 300°$). For the other compounds **53–58** the helix optical activity remains strong. Notably, for **57** a wrong absolute configuration is predicted and **55** and **58** exhibit tremendous deviations between calculated and observed rotations. It should be noted that suitable esters of (1*R*, 2*R*) – (+)-*trans*-chrysanthemic acid (**58**) are potent insecticides, safe to mammals and biodegradable[49]. Referring to the results for *cis*-2-methyl-



(58)

cyclopropane carboxylic acid (**14**) (Table 2), however, the above findings are not unexpected. For **14** a wrong absolute configuration was predicted. This was related to the presence of an unfavorable Me/COOH arrangement. Compounds **55** and **58** contain also such unfavorable *cis*-vicinal Me/COOH arrangements and **57** contains even two such problematic substructures.

As a summary (of the results of Tables 2–4 and those of Ref. 4) one may state that the TTOR approach in its truncated form (equations 2, 3 and 5) gives a satisfying quantitative description of optical rotations of complex cyclopropanes **I**. There are only some very few discrepancies between calculated and observed rotations. The disagreements are mostly due to defined unfavorable ligand orientations which may introduce solvent effects (e.g.

TABLE 3. Calculated (equation 12)[a] and experimental molar rotations of 1, 1-diphenylcyclopropanes (XVIII)[4]

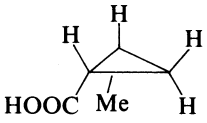
Compound[b]	R^3	R^4	$\Phi_D^{(0)}$ (deg)	$\Phi_D^{(1)}$ (deg)	Φ_D (deg)	$[\Phi]_D$ (deg)	z	Ref.
33	H	Me	+280.50	−27.81	+252.69	+266.6 ($CHCl_3$)	5.2	38
34	H	COOMe	+709.50	−60.46	+649.04	+617.3 ($CHCl_3$)	5.1	35
35	H	CN	+716.10	−53.63	+662.47	+723.2 ($CHCl_3$)	8.4	35
36	H	NC	+841.50	−68.72	+772.78	+665 ($CHCl_3$)[c]; +774.1[d]	16.2	36
37	Me	NC	+561.00	−126.66	+434.34	+335 ($CHCl_3$)[c]; +387.3[d]	30.4	34
38	H	OMe	+330.00	−18.30	+311.70	+92.2 ($CHCl_3$)[c]; +168.2[d]	238.1	39
39	H	Cl	+561.00	−55.76	+505.24	+269.0 ($CHCl_3$)[c]; +490.9[d]	87.8	39
40	Me	Cl	+280.50	−102.93	+177.57	+155.6 ($CHCl_3$)	14.1	32
41	H	Br	+792.00	−80.56	+711.44	+554.6 ($EtOH/H_2O$)	28.3	41
42	Me	Br	+511.50	−148.51	+362.99	+320.5 ($CHCl_3$)	13.3	33
43	Me	I	+801.90	−230.10	+571.80	+573.6 ($CHCl_3$)	0.3	33

[a] In $CHCl_3$, EtOH, or MeOH.
[b] $R^1 = R^6 = Ph$, $R^2 = R^5 = H$.
[c] Estimated according to $[\Phi]_D \approx (\lambda/589)^2 \cdot [\Phi]_\lambda$.
[d] $[\Phi]_{546}$.

TABLE 4. Calculated (equations 2, 3, 5)[a] and observed molar rotations of complex cyclopropanes (I)[4]

Compound	R^1	R^6	R^2	R^5	R^3	R^4	$\Phi_D^{(0)}$ (deg)	$\Phi_D^{(1)}$ (deg)	Φ_D (deg)	$[\Phi]_D$ (deg)	z	Ref.
44	H	Ph	Cl	Cl	Me	H	+425.00	−338.75	+86.25	+261.0($CHCl_3$)	67.0	43
45	H	Ph	Br	Br	Me	H	+715.50	−616.12	+99.38	+237.3($CHCl_3$)	58.3	43
46	H	Ph	H	H	CN	COOMe	−716.10	+214.48	−501.62	−304.4(EtOAc)[c]; −354.2[b]	64.8	44
47	H	Ph	H	H	COOMe	CN	−709.50	+210.62	−498.88	−434.0(EtOAc)[c]; −505.1[b]	14.9	44
48	COOMe	Ph	H	H	COOMe	H	−709.50	+127.24	−582.26	−421.8(MeOH)	38.0	14
49	COOMe	Ph	H	H	H	COOMe	+462.25	−144.30	+317.95	+339.5(MeOH)	6.4	14
50	H	Ph	H	H	CN	CN	−716.10	+218.79	−497.31	−328.1(Me_2CO)[c]; −381.8[b]	51.6	44
51	Cl	H	H	H	COOMe	Ph	+561.00	−113.95	+447.05	+400.3(CH_2Cl_2)	11.7	45
52	Cl	H	H	H	CHO	Ph	+561.00	−168.20	+392.80	+381.2(CH_2Cl_2)	3.0	45
53	COOMe	COOMe	H	H	H	COOMe	+462.25	−211.09	+251.16	+291.4(MeOH)	13.8	14
54	COOMe	H	H	Me	H	COOMe	+279.50	−112.87	+166.61	+214.4(CCl_4)[b]	22.3	46
55	H	Me	H	COOH	Me	H	+90.95	−9.07	+81.88	+27.08(EtOH)	202.4	47
56	H	Me	H	COMe	Me	H	+165.75	−102.76	+62.9	+30.48(EtOH)	106.7	47
57	COOH	H	Me	Me	H	COOH	−42.24	+76.85	+34.61	−52.67(MeOH)	165.7	40
58	H	$HC{=}CMe_2$	COOH	H	Me	Me	+63.64	−22.18	+41.46	+24.06(EtOH)	72.3	48

[a] In $CHCl_3$, EtOH, or MeOH.
[b] $[\Phi]_{546}$.
[c] Estimated according to $[\Phi]_D \approx (\lambda/589)^2 \cdot [\Phi]_\lambda$.



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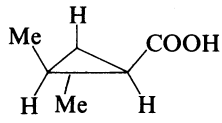

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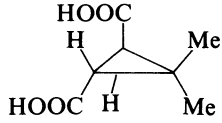
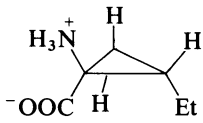


(57)

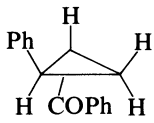
steric hindrance of solvation) or conformational effects (e.g. enforcement of particular ligand arrangements). Hence, a rather secure method for the assignments of absolute configurations of cyclopropanes is available. According to the introductory remarks (Subsection II.A.1) it is not astonishing that optical rotations (and absolute configurations) of cyclopropane amino acids, such as (+)-coronamic acid (**59**)[50], cannot be treated with the simple level of the TTOR approach.



(**59**), $[\Phi]_D + 19.0°(H_2O)$

c. 1,1-*Diphenylcyclopropanes with carbonyl groups*

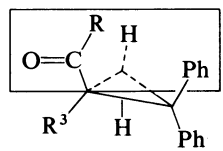
In general, the presence of a carbonyl group, such as CHO or COMe, does not generate serious complications in the theoretical treatment of molar rotations of cyclopropanes (cf. **15**, **16** in Table 2; **52**, **56** in Table 4). It seems that also rotations of cyclopropanes with a benzoyl group can be tackled on the basis of equations 2, 3 and 5. For **60**, for instance, one finds



(**60**)

$$\Phi_D = \Phi_D^{(0)} + \Phi_D^{(1)} = -924.00 + 191.36$$
$$= -732.64°$$
$$[\Phi]_D - 868.0°(Me_2CO)^{51,52}$$

On the other hand, it was found[4] that the molar rotations of 1,1-diphenylcyclopropanes with CHO and COPh groups cannot be described with the procedure used so far. It was suggested[4] that in these compounds an additional rotation contribution in the sense of equation 1 is necessary. This additional rotation term is assumed to be due to a non-negligible optical activity of the carbonyl group ('ligand optical activity') in the particular molecular environment. In terms of the TTOR approach in such cyclopropanes **XIX** a further element of optical activity transforming like a polar plane is relevant. The



(**XIX**)

generation of the chiral plane in **XIX**, i.e. the induction of asymmetry in the electron density distribution of the substituent COR, can be explained by the existence of a preferred (*trans* or *cis*) bisected (or nearly bisected) conformation of COR. For such an arrangement COR lies in a mirror plane of the D_{3h} cyclopropane skeleton.

The asymmetry in the electron density distribution of COR, hence, is induced by lifting the local C_s symmetry of COR by the geminal phenyl rings and H atoms, respectively. These geminal groupings lie above or below the plane of COR. As in **XIX** R^3 lies in the relevant polar plane, it should not affect the chirality of the electron density distribution of COR significantly. Therefore, the rotation contribution from the ligand COR should be (almost) independent from the substituent at site 3. As a first approximation the rotation contribution from COR therefore can be viewed as a constant. In this way the molar rotations of 1,1-diphenylcyclopropanes **XIX** are described by equation 13[4].

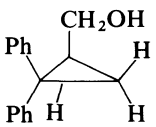
$$\Phi_D(\mathbf{XIX}) = \Phi_D^{(0)} + \Phi_D^{(1)} + \Phi_D^{(2)} \tag{13}$$

In equation 13 $\Phi_D^{(0)}$ and $\Phi_D^{(1)}$ have the usual meanings (and are given by equations 3 and 5). For the constant rotation term $\Phi_D^{(2)}$ (which is affected only by R) equations 14a and 14b apply[4].

$$\Phi_D^{(2)} = \begin{cases} \Phi_D^{CHO} = -475° & \text{(CHO at site 4)} \quad (14a) \\ \Phi_D^{COPh} = -500° & \text{(COPh at site 4)} \quad (14b) \end{cases}$$

Theoretical and experimental molar rotations of 1,1-diphenylcyclopropanes **XIX** with carbonyl substituents are given in Table 5. Though the agreements between Φ_D and $[\Phi]_D$ for **XIX** are inferior to the previous ones in Tables 2–4 the above method gives correct absolute configurations in all the cases. The less satisfying numerical predictions probably result from the neglection of the influence of R^3. The role of the COR groups for the optical activity of 1,1-diphenylcyclopropanes **XIX** will be discussed further in the subsequent subsection (II.A.3.d) in the context of ORD of cyclopropanes.

A final remark about effects of steric hindrance of solvation of polar groups shall complete the discussion of optical rotations at the wavelength of the sodium-D-line. It seems that the truncated TTOR approach (equations 2, 3 and 5) remains valid for 1,1-diphenylcyclopropanes, if the target group for solvation (such as COOH or CH_2OH) is sterically not strongly hindered[4]. This is seen from the calculated and observed rotations of **71–74**.



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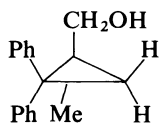

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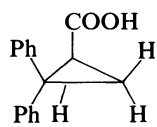

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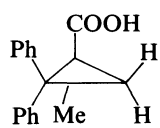


(74)

Compound	$\Phi_D^{(0)}$ (deg)	$\Phi_D^{(1)}$ (deg)	Φ_D (deg)	$[\Phi]_D$ (deg)[a]	Ref.
71	+395.70	−31.75	+327.95	+374.6	11
72	+79.20	−2.96	+76.24	−76.3	11
73	+633.60	−59.21	+574.39	+548.1	11, 35
74	+353.10	−109.45	+243.65	−89.4	11, 33

[a] In chloroform.

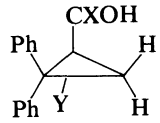
TABLE 5. Calculated (equations 13, 14)[a] and experimental molar rotations of 1,1-diphenylcyclopropanes (**XIX**)[b] with carbonyl groups[4]

Compound	R^3	R^4	$\Phi_D^{(0)}$ (deg)	$\Phi_D^{(1)}$ (deg)	$\Phi_D^{(2)}$ (deg)	Φ_D (deg)	$[\Phi]_D$ (deg)	z	Ref.
61	H	CHO[c]	+924.00	−54.91	−475	+394.09	+256.3($CHCl_3$)	53.8	11
62	Me	CHO[c]	+643.50	−101.44	−475	+67.06	+189.8($CHCl_3$)	64.7	11
63	OMe	CHO[c]	+594.00	−86.36	−475	+32.64	+67.7($CHCl_3$)[e]; +123.6[f]	54.2	39
64	F	CHO[c]	+660.00	−31.42	−475	+153.58	+215.9(dioxane)[e]; +394.1[f]	28.9	39
65	Cl	CHO[c]	+363.00	−0.10	−475	−112.10	−215.2($CHCl_3$)[e]; −392.8[f]	47.9	39
66	Br	CHO[c]	+132.00	−0.61	−475	−343.61	−515.5($CHCl_3$)	33.3	11
67	Me	COPh[d]	+643.50	−126.27	−500	+17.23	+103.1($CHCl_3$)	83.3	38a
68	OMe	COPh[d]	+594.00	−107.51	−500	−13.51	−56.3($CHCl_3$)[e]; −102.7[f]	76.0	39
69	F	COPh[d]	+660.00	−39.11	−500	+120.89	+65.9($CHCl_3$)[e]; +120.2[f]	83.4	39
70	Cl	COPh[d]	+363.00	−0.10	−500	−137.10	−229.2($CHCl_3$)	40.2	39

[a] In $CHCl_3$, EtOH, or MeOH.
[b] $R^2 = R^5 = H$, $R^1 = R^6 = Ph$.
[c] Equation 14a.
[d] Equation 14b.
[e] Estimated according to $[\Phi]_D \approx (\lambda/589)^2 [\Phi]_\lambda$.
[f] $[\Phi]_{436}$.

If the CXOH (X = O, H_2) substituent has no geminal group (**71**, **73**), the rotations can be predicted correctly. With a methyl group geminal to CXOH the TTOR approach fails. In **72** and **74** the CXOH group is strongly shielded.

Complications in the treatment of optical rotations have also been observed for 1,1-diphenylcyclopropanes of the type **XX**[4]. Here, however, probably intramolecular hydrogen bonds between geminal groups are responsible for the breakdown of the TTOR approach.



X = O,H_2
Y = OMe,Cl,Br

(XX)

d. Optical rotatory dispersion

In the TTOR approach for the description of optical rotatory dispersion (ORD) in the transparent region (Φ_λ, $\lambda \geqslant 330$ nm) for each term $\Phi_\lambda^{(i)}$ in equation 1 endogenous and exogenous variables are separated. For the helix optical activity, for instance, one has equation 15[3,4].

$$\Phi_\lambda^{(0)} = c(\lambda, \lambda_0) \cdot \Phi_D^{(0)} \tag{15}$$

The approximation 15 means that the variables associated with the molecular system (the expression containing the system's parameter λ(R)) and the variable λ (the wavelength of the incident light) which is under the control of the observer are separated. In general, equation 15 does not mean that the system parameters λ(R) do not depend upon the wavelength. The approximation 15 means that the expression $\Phi_D^{(0)}$ containing differences between the various parameters, such as $[\lambda(R^1) - \lambda(R^2)]$, exhibit, if at all, only little wavelength dependence.

In equation 15 $\Phi_D^{(0)}$ corresponds to the rotation contribution at the wavelength of the sodium-D-line (given by equation 3 and the parameters of Table 1). The factor c depends upon a particular constant λ_0 which may be zero. The factor c may have various analytical forms [3,4,16]. Generally $c(\lambda, \lambda_0)$ is a hyperbolic function of λ. Furthermore, the parametrization for the rotation contribution $\Phi_D^{(0)}$ is done in such a way that $c(\lambda, \lambda_0)$ obeys the normalization condition (equation 16).

$$c(\lambda_D, \lambda_0) = 1 \tag{16}$$

For cyclopropanes **I** the ORD of the helix term is given by equation 17[4].

$$\Phi_\lambda^{(0)} = \frac{\lambda_D^2 - \lambda_0^2}{\lambda^2 - \lambda_0^2} \cdot \Phi_D^{(0)} \tag{17}$$

The empirical constant λ_0 is related to the groups attached to the molecular skeleton. This means that each ligand R^i is associated with a particular value of λ_0. However, only one constant λ_0 will be used in equation 17. And this constant λ_0 is determined empirically by that group R^i of **I** (with the six ligands R^1, . . . R^6) which has the greatest λ_0-value. For λ_0 equation 18 applies[4].

$$\lambda_0 = \begin{cases} 195 \text{ nm for R = H, alkyl, } CH_2X, (CH_2)_2X, CN \\ 212 \text{ nm for R = COOH, COOMe, } H_2C{=}CH, H_2C{=}CMe, Me_2C{=}CH \\ 228 \text{ nm for R = Ph} \end{cases} \tag{18}$$

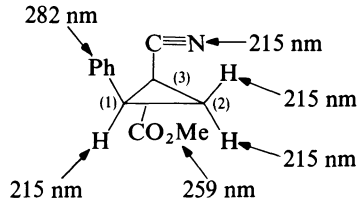
According to the above rule, for instance, one has to select $\lambda_0 = 228$ nm for compound **20** (Table 2) and also $\lambda_0 = 228$ nm for **24** (Table 2). The description of the ORD of the atomic asymmetry term $\Phi_\lambda^{(1)}$ is more complicated. Each of the three terms $\varphi_{\lambda(k)}^{(1)}$ (representing the ORD of the three asymmetric carbon atoms (k) ($k = 1, 2, 3$) of **I**) may exhibit a different wavelength dependence according to equation 19[4].

$$\varphi_{\lambda,(k)}^{(1)} = \frac{\lambda_D^2 - \lambda_1^{(k)}}{\lambda^2 - \lambda_1^{(k)}} \cdot \varphi_{D,(k)}^{(1)} \qquad (k = 1, 2, 3) \tag{19}$$

In equation 19 $\varphi_{D,(k)}^{(1)}$ is one of the three rotation contributions in equation 5 which describes C_{2v}-tetrahedral optical rotation at the wavelength of the sodium-D-line. The constant $\lambda_1^{(k)}$ will be determined by the groups not directly attached to the particular asymmetric carbon atom. For instance, in **I** $\lambda_1^{(1)}$ will depend on R^3, R^4 and R^2, R^5. This means that $\lambda_1^{(k)}$ depends upon those ligands which appear in the v(R)-term of equation 5. For $\lambda_1^{(k)}$ it was found that equation 20 applies[4].

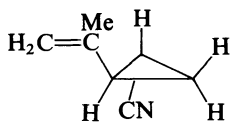
$$\lambda_1^{(k)} = \begin{cases} 215 \text{ nm} \\ 259 \text{ nm} \\ 282 \text{ nm} \end{cases} \quad \begin{array}{l} \text{for R appearing} \\ \text{in } v\text{(R) and} \end{array} \quad \begin{array}{l} \text{R = H, alkyl, } CH_2X, (CH_2)_2X, CN \\ \text{R = COOH, COOMe, } HC{=}CR'_2 \\ (R' = H, Me), H_2C{=}CMe \\ \text{R = Ph} \end{array} \tag{20}$$

As for the helical term, in equation 19 the constant $\lambda_1^{(1)}$ of carbon atom (1) corresponds to the largest value of the set of $\lambda_1^{(k)}$-values provided by the ligands attached to the other carbon atoms (2) and (3). For instance, for **47** one has $\lambda_1^{(1)} = 259$ nm, $\lambda_1^{(2)} = 282$ nm and $\lambda_1^{(3)} = 282$ nm.

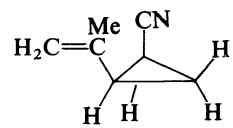


(47)

The important consequence of the above theoretical treatment of ORD of cyclopropanes **I** is that the compounds may show anomalous rotatory dispersions in the transparent region. This means that the rotations of some cyclopropanes **I** may change their signs in the long wavelength region $\lambda \geqslant 400$ nm. This, indeed, is observed for some cyclopropanes. For instance, the *trans* compound **75** exhibits a plain ORD curve, whereas the rotation of the *cis*-cyclopropane **76** inverses its sign[53]. The particular ORD behavior of **75** and **76** is reproduced by the TTOR approach using the wavelength dependences given by equations 17–20[4].



(75)

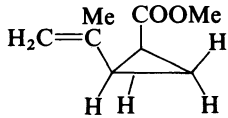


(76)

(75)	589 nm	365 nm
Φ_λ (deg)	−190.98	−530.45
$[\Phi]_\lambda$ (deg)	−218.0	−742.9 (C_6H_{12})

(76)	589 nm	365 nm
Φ_λ (deg)	+3.73	−100.8
$[\Phi]_\lambda$ (deg)	+4.74	−53.3 (C_6H_{12})

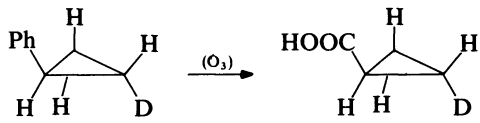
The result for **76** can be anticipated qualitatively, as the rotation of **76** results from only atomic asymmetry ($\Phi_\lambda^{(1)}$) and the groups CN and $MeC{=}CH_2$ induce different $\lambda_1^{(k)}$-values (215 nm vs. 259 nm) in the ORD equations 19 for $\varphi_{\lambda,(1)}^{(1)}$ and $\varphi_{\lambda,(3)}^{(1)}$. As, on the other hand, the *cis* compound **77** has only groups with equal $\lambda_1^{(k)}$-values (259 nm), one may infer qualitatively that **77** should have a plain ORD curve in the transparent region. This, indeed, is observed[53].



(77)

$[\Phi]_D$ −19.7° (MeOH)
$[\Phi]_{365}$ −89.3° (MeOH)

Sign inversion of the optical rotation in the transparent region is also found for the deuterated cyclopropanecarboxylic acid **78** which is obtained from *trans*-1-phenylcyclopropane-2-d (**79**) through oxidation[54]. (The minimum molar rotation of **79** will be given in Subsection II.B.2; the optical purity of **78** is unknown).

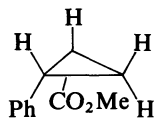


(79) (78)

α_{365} −1.112°
(neat, 1 dm)

α_D +0.110°
α_{405} −0.212°
(neat, 1 dm)

With the above theoretical procedure whole ORD curves can be easily calculated, for instance, that of *cis*-methyl 2-phenylcyclopropane-1-carboxylate (**25**)[28]. For that phenylcyclopropane the fit becomes inferior for $\lambda < 400$ nm, i.e. for rotations coming closer to the light absorption region of the compound.



(25)

	589 nm	546 nm	500 nm	436 nm	400 nm	365 nm
$[\Phi]_D$	−89.87	−111.55	−148.38	−229.09	−310.15	−449.36
Φ_D	−72.93	−87.99	−110.39	−169.74	−202.07	−285.93
$1.232 \times \Phi_D$	−89.87	−108.43	−136.03	−209.17	−249.17	−352.35

Further optical rotations of cyclopropanes measured at different wavelengths in the transparent region are found in Refs 10a–10c, 15b, 28, 36, 41, 53.

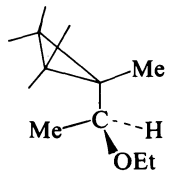
ORD curves extending into the absorption region are reported in the literature for 1,1-diphenylcyclopropanecarboxaldehydes **61**, **62**[11] and **63**–**65**[39]. These aldehydes exhibit Cotton effect ORD curves. Changes of the signs of the rotations occur near 300 nm for **62**, **63** and **65**. **61** and **64** show Cotton effect curves without sign inversions.

The ORD curves of the aldehydes **61**–**65** corroborate the treatment of the optical rotations of these compounds according to equations 13 and 14. In terms of quantum-theoretical treatments of ORD[1] the rotation contribution of the carbonyl group, $\Phi_D^{(2)} = \Phi_D^{CHO}$, results from the optical activity of the (n, π^*) electronic transition of that group. The (n, π^*) transition of 1,1-diphenylcyclopropanecarboxaldehydes is found between 287 nm and 304 nm[11,39]. Inspection of the ORD curves of these last aldehydes (Figure 3) reveals that each one exhibits a negative (n, π^*) Cotton effect near 300 nm giving a negative rotation contribution Φ_D^{CHO} at 589 nm. Onto the negative (n, π^*) ORD curve a positive one (resulting from $\Phi_D^{(0)} + \Phi_D^{(1)}$) is superimposed.

B. Optical Rotations of Miscellaneous Compounds

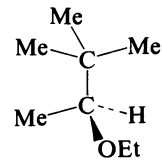
1. Alkylidenecyclopropanes and bicyclic cyclopropanes

So far, optical rotations of compounds have been discussed where the optical activity is associated with the particular structure of the cyclopropane ring. This means that the rotations are generated by a chiral arrangement of (achiral) ligands attached to the (achiral) molecular skeleton. For certain substituent patterns of **I**, in particular, the rotations are induced by atomic asymmetry. This is true for **III** and **IV**. The effect of the (achiral) cyclopropane moiety (viewed as a ligand) on open-chain molecules with an asymmetric carbon atom can be seen from the rotations of (*S*)-(−)-1-methyl-1-(1-ethoxyethyl) cyclopropane (**80**) and its counterpart **81** with only acyclic substituents[55].



(80)

$[\Phi]_D - 10.9°(CCl_4)$



(81)

$[\Phi]_D + 29.2°(CCl_4)$

From the data for **80** and **81** one can see that the methylcyclopropyl group and the open-chain analogous group, *t*-butyl, have different effects on the rotation induced by an asymmetric carbon atom (provided both the groups rotate freely in **80** and **81**). Compounds **80** and **81** of equal absolute configurations exhibit different signs for their rotations.

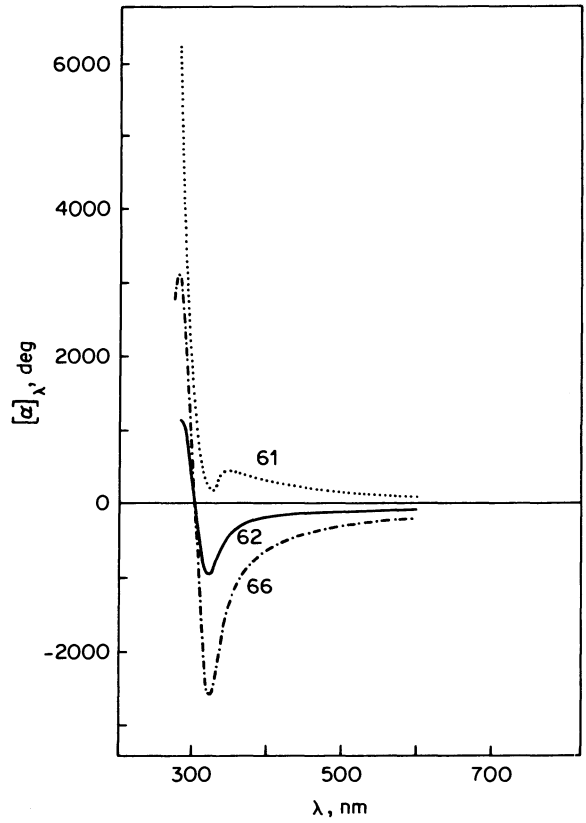
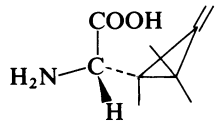


FIGURE 3. ORD–curves (dioxane) of (+)-2,2-diphenylcyclopropanecarboxaldehyde (**61**), (−)-1-methyl-2,2-diphenylcyclopropanecarboxaldehyde (**62**), and (−)-1-bromo-2,2-diphenylcyclopropanecarboxaldehyde (**66**)[11]. *Reprinted with permission from Walborsky* et al., J. Am. Chem. Soc., **83**, *2517, Copyright (1961) American Chemical Society*

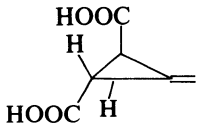
If one analyzes the rotation of D-α-(methylenecyclopropyl)glycine (**82**)[56] the optical activity must come from (at least) four sources. One rotation contribution is associated with the atomic asymmetry of the open-chain moiety (methylenecyclopropane being viewed as a ligand). On the other hand, optical activity will also be induced by the asymmetric carbon atom of the ring and the asymmetry in the electron density distribution of the exocyclic double bond system (with diastereotopic faces). Finally also helix optical activity may be operative. The example of **82** demonstrates the complexity of the optical rotation of an apparently simple cyclopropane derivative. Further discussions of optical rotations of similar compounds, therefore, will cling to only the qualitative level.

Alkylidenecyclopropanes exhibit, in general, rather large optical rotations, as is revealed by the data for the compounds **83–85** related to Feist acid (**83**)[46,57,58].

It is apparent that the polar groups COOR (R = H, Me) exert a more pronounced effect on the rotations than the methyl group does. Remembering that helical rotation

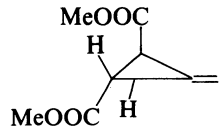


(82) $[\Phi]_D - 106.0°(H_2O)$
$-139.9°$ (5N HCl)



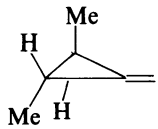
(83)

$[\Phi]_{546} + 250.1°$ (EtOH)[46]
$[\Phi]_D + 212.3°$ (EtOH)



(84)

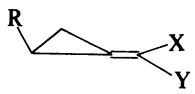
$[\Phi]_{546} + 246.7°(CCl_4)$



(85)

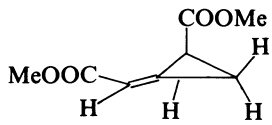
$[\Phi]_D + 48.8°(CCl_4)$

contributions are generally rather large one can hypothesize that for the generation of optical rotations of alkylidenecyclopropanes **XXI** allylic (helical) subunits with the end-groups R/X or R/Y, respectively, will have a decisive influence.



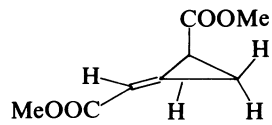
(XXI)

This is also suggested by the data of *syn*- and *anti*-2-carbomethoxy-1-(carbomethoxymethylene)cyclopropane (**86**, **87**)[46]. Changing the position of the carbomethoxy group at the double bond (*syn* (**86**) → *anti* (**87**)) makes the rotation more negative by *ca.* 300°. Though only minimum rotations for the compounds are known, one can assume that the samples of **86** and **87**, obtained from thermal isomerization of **84**[46], have the same optical purities. Hence, the comparison between the rotation values below is justified. (Optically pure **86** should have $[\Phi]_D + 229.7°$[46].)



(86)

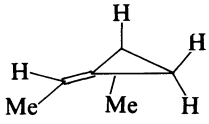
$[\Phi]_D^{min} + 188.9°(CCl_4)$



(87)

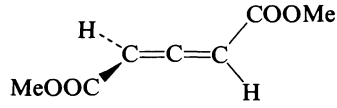
$[\Phi]_D^{min} - 102.1°(CCl_4)$

The effect of a methyl group on the rotation of alkylidenecyclopropanes also remains small compared with the influence of a carbomethoxy group, if the methyl group is attached to the double bond. This can be seen from the rotations of **87** and **88** (which are at least 80% optically pure)[58b]. As has been pointed out, a double bond and a three-membered ring at the corresponding position have similar effects on chemical and physical



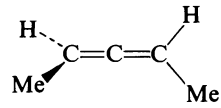
(**88**), $[\Phi]_D + 8.79°$ (CCl_4)

properties. Therefore, one could, for instance, try to compare the rotations of the methylenecyclopropanes **87** and **88** with those of the corresponding allenes **89** and **90**[22].



(**89**)

$[\Phi]_D - 376°$ (EtOH)

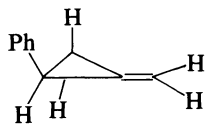


(**90**)

$[\Phi]_D + 53.3°$ (neat)

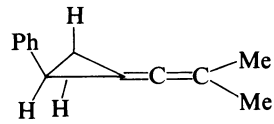
Though such a comparison cannot reflect more than a very crude relationship between the magnitudes of the optical rotations, it is to be noted that the absolute configurations of correspondingly substituted methylenecyclopropanes and allenes are identical. However, owing to the small number of examples one cannot be sure about the generality of the above rule for the deductions of absolute configurations of methylenecyclopropanes. The limit for comparisons between optical rotations of methylenecyclopropanes and allenes can be seen from compound **91** which shows a distinct rotation. The corresponding allene, $PhHC{=}C{=}CH_2$, however, is achiral and has a zero rotation.

The effect of the type of unsaturated moiety exocyclic to a cyclopropane ring on the optical rotation is demonstrated by the methylenecyclopropane **91**[15a] and the vinylidenecyclopropane **92**[31]. Both compounds have the same absolute configuration, (R)-(−).



(**91**)

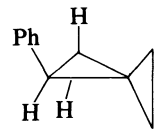
$[\Phi]_D - 45.6°$ ($CHCl_3$)



(**92**)

$[\Phi]_D - 113.7°$

Neglecting the effects of the methyl groups as a first approximation the rotation of **92** is more than twice that of **91**. As the cyclopropane ring can be compared with a double bond[17, 20], phenylspiropentane (**93**) can also be compared with **91** and **92**. The rotation of

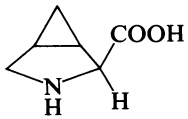


(**93**)

$[\Phi]_D - 79.3°$ ($CHCl_3$)

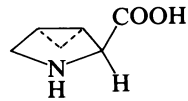
93[15a] is intermediate between those of **91** and **92**. This is unexpected as, if one refers to the degree of unsaturation, **93** should have the smallest rotation of the triple **91–93**.

Finally, the rotations of some more bicyclic cyclopropanes shall be considered. The emphasis will be on the effect of the cyclopropane moiety on the rotations of some selected systems. At first, *cis*- and *trans*-3,4-methylene-L-proline (**94**, **95**) shall be compared with



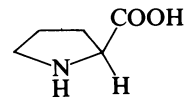
(**94**)

$[\Phi]_D - 119.5°(H_2O)$



(**95**)

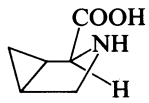
$[\Phi]_D - 166.6°(H_2O)$ synthetic
$-183.1°(H_2O)$ natural



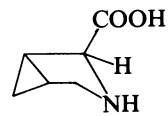
(**96**)

$[\Phi]_D - 100.1°(H_2O)$

proline (**96**). An interesting feature of the *cis* and *trans* acids **94** and **95** is that in both compounds the six-membered ring achieves the boat conformation[59]. In the *trans* acid **95** the carboxy group is axial to the ring, whereas in **94** it has an intermediate position between axial and equatorial[59]. Using the rotation of proline (**96**)[60] as a basis it is seen that the

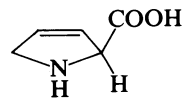


(**94**)



(**95**)

rotation is little altered if the cyclopropane moiety is attached *cis* to the carboxy group (**94**). On the other hand, the *trans* attachement of the cyclopropane ring in **95** has a rather pronounced effect on the optical rotation. An interpretation of this finding is not straightforward, because the steric shielding of the COOH group (and corresponding solvent effects) in **94** will alter the situation relative to that of **95**. On the other hand, it is justified to compare the rotations of **95**, **96**, and 3,4-dehydroproline (**97**)[97].



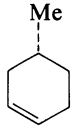
(**97**)

$[\Phi]_D - 359.7°(H_2O)$

In the trans compound **95** the carboxy group is not sterically hindered and, hence, the cyclopropane ring will influence the optical rotation essentially via its electronic effect. In the series **95–97** the rotations increase and, as expected, the cyclopropane ring acts similar to an endocyclic double bond. It increases the rotation of **96**. The magnitude of the effect, however, is smaller than that of the double bond. The similarity of the three-membered ring and an endocyclic double bond can also be utilized when relating the rotations of (*R*)-(+)-4-methylcyclohexene (**98**)[61] and (−)-*cis*-carane (**99-*c***)[62, 63] and (+)-*trans*-carane (**99-*t***)[63–65] to their absolute configurations. In the *trans* compound **99-*t*** the Me group and the cyclopropane ring do not interfere sterically. Hence, **98** and, at least, **99-*t*** with the same

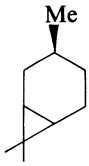
absolute configurations should have rotations with the same signs and similar orders of magnitude, as is observed.

The 'conjugation effect' of the cyclopropane ring on optical rotation can also be seen in other situations. If in bicyclic compounds the cyclopropane moiety comes into α,β-position relative to a double bond, a marked increase in the magnitude of the rotation is observed. This can be demonstrated referring to (−)-*cis*-carane (**99-c**), (+)-*trans*-carane (**99-t**) and the *cis* and *trans* compounds **100-c**[66] and **100-t**[66].



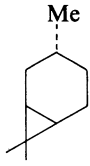
(**98**)

$[\Phi]_D + 102.9°$(MeOH)



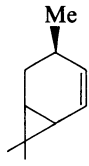
(**99-c**)

$-24.6°(CHCl_3)$



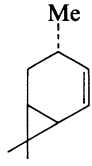
(**99-t**)

$+56.1°$(neat)



(**100-c**)

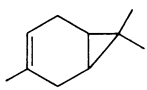
$-220.1°(C_6H_6)$



(**100-t**)

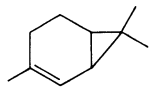
$-228.2°(C_6H_6)$

For both the couples **99-c**, **100-c** and **99-t**, **100-t** the rotations become more negative by more than 200°. The effect of the conjugation of the cyclopropane ring with the C=C double bond on the optical rotation is also seen for the compounds **101**[65] and **102**[62]. Here, both the compounds have the same degree of unsaturation. Insulating a CH_2-group between the double bond and the cyclopropane ring reduces the magnitude of the optical rotation of **102** considerably.



(**101**)

$[\Phi]_D + 22.3°$ (neat)

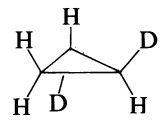


(**102**)

$[\Phi]_D + 104.0°(CHCl_3)$

2. *Deuterated cyclopropanes*

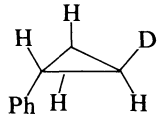
Isotopic substitution, in particular, deuteration of the cyclopropane ring, induces small but distinct effects on the optical rotation. The simplest chiral deuterated compound is cyclopropane-1,2-d_2 (**103**)[67,68] (which was obtained from **79** with $\alpha_{365} - 1.112°$(neat, 1dm)). For **103** no specific rotation is available, as the density is not known.



(**103**)

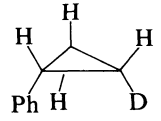
$\alpha_{365} + 0.168°$
(neat, 1 dm)

For the *trans*- and *cis*-2-deuterio-1-phenylcyclopropanes (**104**, **105**)[68] the rotations have the same signs and, notably, the *cis* compound **105** exhibits a larger rotation than the *trans* compound **104**. For all the other phenylcyclopropanes the *trans* compounds have rotations with larger magnitudes (Table 2).



(104)

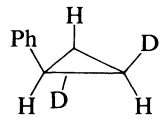
$[\Phi]_D + 3.00°$ (isooctane)



(105)

$[\Phi]_D + 6.90°$(isooctane)

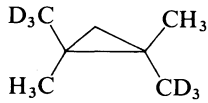
Increasing the number of deuterium atoms at the cyclopropane ring has no significant effect on the optical rotation. For instance, *trans*-1-phenylcyclopropane-2,3-d_2 (**106**)[69] exhibits a rotation value in line with those of the other phenyl compounds. The effect of



(106)

$\alpha_D + 1.38°$ (neat, 1 dm)

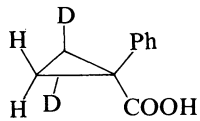
deuteration in a substituent on the optical rotation is comparable with that if deuteration takes place directly at the cyclopropane ring. This is demonstrated by the rotation of tetramethylcyclopropane-d_6(**107**)[70] (of unknown absolute configuration) with a *trans* arrangement of the CD_3-groups.



$[\Phi]_D + 0.57°$ (isooctane)
$[\Phi]_{365} + 3.83°$(isooctane)

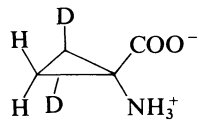
(107)

The cumulative effect of two geminal deuterium atoms attached to the ring is seen from the rotations of **108** and **109**[45].



(108)

$[\Phi]_D + 2.58°(CH_2Cl_2)$

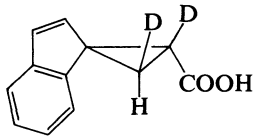


(109)

$[\Phi]_D - 0.90°(H_2O)$

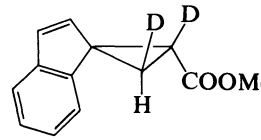
More interesting with regard to the effect of esterification on the rotation than with respect to the effect of deuteration are the recently synthesized optically active deuterated acid **110** and its ester **111**[71]. Generally, the rotations of acids and their corresponding esters (measured in the same solvent) differ by no more than 39 % (cf., for instance, **83** and **84**, **34** (Table 3) and **73**). The data of **110** and **111** may be taken as a further demonstration of the role of the solvent on optical rotations of cyclopropanecarboxylic acids, in particular, steric hindrance of solvation of the COOH group.

Rotations of more deuterated cyclopropanes can be found in Refs 72 and 73.



(110)

$[\Phi]_{546} - 445.1°(CHCl_3)$



(111)

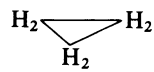
$[\Phi]_{546} - 253.8°(CHCl_3)$

III. ELECTRONIC CIRCULAR DICHROISM OF CYCLOPROPANES

A. The Cyclopropane Chromophore and the Circular Dichroism of Cyclopropane Hydrocarbons

Electronic circular dichroism (CD) results from different absorption (molar absorption coefficient ε_l and ε_r) of left- and right-circularly polarized light by the electronic subsystem of the molecule. CD has the same electronic origin as ordinary absorption. Therefore, CD spectra are interpreted in terms of the same concepts as absorption spectra, namely electronic transitions and excited states of definite 'chromophores'[1]. For the discussions of electronic structures and excitations of complex chromophores molecular orbital (MO) theory provides an adequate framework.

The relevant electronic features of the cyclopropane chromophore, in particular, the unusual conjugation properties of cyclopropane (**112**) can be discussed referring to those



(112)

orbitals of **112** which are given in Figure 4. In the schematic orbital diagram the MOs $3a_1'$, $3e'$, $4e'$, and $1a_2'$ correspond to the Walsh representation of MOs of **112**. In the symmetry group D_{3h} of **112** the irreducible representations are associated with a prime to denote symmetric transformation properties under the generating element σ_h (mirror plane reflection) of the group. The double prime denotes antisymmetric transformation properties.

In the one-electron excitation picture the lowest energy excited valence-shell singlet states result from $3e' \rightarrow 4e'$, $3e' \rightarrow 1a_2'$, and $1e'' \rightarrow 4e'$ electronic transitions[74–78]. In cyclopropane (**112**) the HOMO → LUMO ($3e' \rightarrow 4e'$) excitation shows a certain similarity with the HOMO → LUMO ($1e_{1g} \rightarrow 1e_{2u}$) transition of benzene[79]. In **112** the ($3e' \rightarrow 4e'$) (vertical) excitation generates three electronic excited singlet states $^1A_1'$, $^1A_2'$, $^1E'$. The doubly degenerate $^1E'$ excited state is electric allowed and polarized in the plane of the molecule. The $^1A_1'$ and $^1A_2'$ excited states have vanishing transition moments. In benzene the analogous electronic $1e_{1g} \rightarrow 1e_{2u}$ transition results in the (singlet) excited states $^1B_{2u}$, $^1B_{1u}$, $^1E_{1u}$, the doubly degenerate state $^1E_{1u}$ being electric allowed and polarized in the plane of the molecule. The non-degenerate states $^1B_{2u}$ and $^1B_{1u}$ have no electric transition moments.

In addition to the above valence-shell transitions it may be that within the manifold of low energy excited states also those derived from the $1e'' \rightarrow 4e'$ excitation can be found. Inspection of Figure 4 reveals that the states ($^1A_1''$, $^1A_2''$, $^1E''$) resulting from $1e''$ $\rightarrow 4e'$ involve 'perpendicular' $p_z \rightarrow p_x$ (p_y) atomic transitions. Such excitations resemble (n, π^*) transitions of carbonyl functionalities. Hence, there may also exist electric

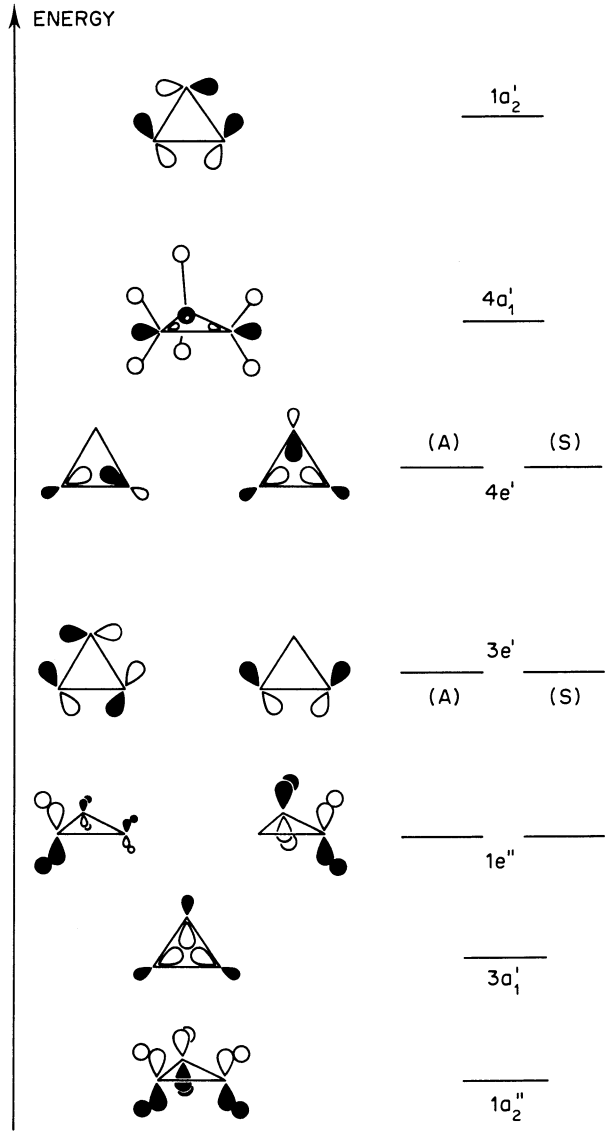


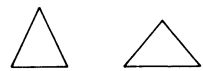
FIGURE 4. Molecular orbital diagram for cyclopropane (**112**) (the Walsh orbitals $3a'_1$, $3e'$, $4e'$, $1a'_2$ being displayed in the xy plane)

forbidden, magnetic allowed transitions of the last type in the low energy spectral region of cyclopropane. Furthermore, in the low energy region Rydberg transitions may also be found. Their energies are given by equation 21.

$$h\nu = I_v - \frac{R}{(n-\delta)^2} \tag{21}$$

In equation 21 R corresponds to the Rydberg constant, n is the principal quantum number and δ the quantum defect. I_v corresponds to the ionization energy of the particular compound. The lowest energy Rydberg transitions of **112** originate with the 3e′ HOMO which has a vertical ionization energy of $I_v = 10.53$ eV[75]. In the PE spectrum of **112** the lowest energy (3e′) PE band is split as a result of Jahn–Teller (JT) distortion of the molecular ion. For the JT distortion two cations of similar energies with C_{2v} symmetry are calculated[80]. In **112a** the system has two long C–C bonds and one short C–C bond, whereas in **112b** two short and one long C–C bond exist. Correspondingly, there may exist two 3e′ → 3s Rydberg transitions which result from the two JT components of the ionized 3e′ orbital.

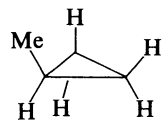
All the above considerations reveal that the absorption spectrum of **112** will be a complexity of overlapping bands and, therefore, the assignment of electronic features of the absorption spectrum of **112** is still far from being clear. This also complicates the discussion of the CD of the cyclopropane chromophore.



(112a) **(112b)**

The longest wavelength absorption of **112** is centered around 54 000 cm^{-1}. This is a very weak band ($\varepsilon \approx 10$)[74] and should be associated with the $^1A_2'(3e' \rightarrow 4e')$ excited state[76b]. In solution the absorption then rises to a medium intense band at ca. 70 000 cm^{-1} and reaches an intense maximum at ca. 83 000 cm^{-1}. In the gas phase two structured bands appear at 62 000 cm^{-1} and 76 000 cm^{-1}. According to equation 21 these bands result from 3e′ → 3p and 3e′ → 4p Rydberg transitions ($\delta = 0.68$)[75]. As expected for a Rydberg band the 62 000 cm^{-1} band disappears going from the gas phase to the condensed phase.

In methylcyclopropane (**113**) two narrow weak bands appear at 48 383 cm^{-1} and 49 468 cm^{-1} [74]. As a methyl substituent generally destabilizes the HOMO of a given



(113)

molecule by 0.5–0.7 eV, the corresponding excitation should originate with the 3e′ HOMO. Hence, the data for **113** support the assignment of the lowest energy band of **112** to $^1A_2'$.

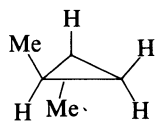
On the basis of literature data, the most likely assignments of electronic bands to excited states of cyclopropane (**112**) (referring to only vertical electronic transitions) are given in Table 6. So far, the lowest energy Rydberg transition 3e′ → 3s of **112** has not been assigned. Using equation 21 and taking $\delta \approx 1.00$ (as is common for ns Rydbergs) one can estimate to find the hitherto not identified 3e′ → 3s Rydberg near 56 000 cm^{-1}, i.e. overlapping with $^1A_2'$. From the data in Table 6 one can infer that in solution CD bands of the cyclopropane chromophore with $\tilde{\nu} \leqslant 60\,000$ cm^{-1} should result from the valence-shell $^1A_2'(3e' \rightarrow 4e')$ and Rydberg 3e′ → 3s transitions.

In Figure 5 the optical rotatory dispersions and CD spectra of some *trans*-disubstituted cyclopropane hydrocarbons are displayed[81]. Compound **1** has C_2 symmetry and with respect to the cyclopropane subunit also **114** and **115** have a local C_2 symmetry. *Trans*-1,2-dimethylcyclopropane (**1**) exhibits a continuous CD rising to a positive Cotton effect

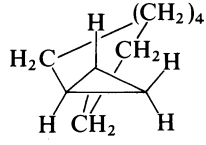
TABLE 6. Excited states' energies of cyclopropane (**112**)[74-76]

State	Character[a]	Energy (cm^{-1})	Intensity
$^1A_2'$ ($3e' \rightarrow 4e'$)	VS	54 000	Very weak
$3e' \rightarrow 3s$	R	56 000	Very weak
$3e' \rightarrow 3p$	R	62 000	Medium
$^1E'$ ($3e' \rightarrow 4e'$)	VS	70 000	Medium
$3e' \rightarrow 4p$	R	76 000	Medium
$3e' \rightarrow 5p$	R	81 000	Strong
$^1E'$ ($3e' \rightarrow 1a_2'$)	VS	83 000	Strong

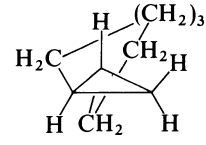
[a] VS, valence-shell transition; R, Rydberg transition.



(**1**)



(**114**)



(**115**)

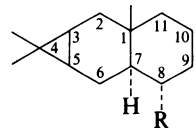
below 190 nm (52 600 cm^{-1}). On the other hand, the zero crossing of the ORD of **114** reveals a positive Cotton effect at 54 000 cm^{-1}. The most interesting CD features are shown by **115**. In Ref. 81 it has been suggested that the torsional strain of **115** is the reason for the particular CD shape and the manifestation of CD bands with lower energies than those of **1** and **114**. Compound **115** (with a maximum optical purity of 72.5%) has a positive CD band at 190 nm (52 600 cm^{-1}; $\Delta\varepsilon \approx +2.5$) and a weak negative CD at 208 nm (48 000 cm^{-1}; $\Delta\varepsilon \approx -0.1$)[81]. According to the data in Table 6 the two bands of **115** may correspond to the $^1A_2'$ valence-shell excited state (48 000 cm^{-1}) and the $3e' \rightarrow 3s$ Rydberg transition. However, a definite assignment should be deferred until more thorough investigations are available.

For the deductions of absolute configurations of cyclopropane hydrocarbons from CD measurements there seems to exist a qualitative rule[81]. Apparently, *trans*-dialkylcyclopropanes (and probably also other polyalkylated chiral cyclopropanes with at least local symmetry C_2) will exhibit a positive Cotton effect between 180 nm and 190 nm for molecules with a structure corresponding to (1*R*, 2*R*)-(−)-*trans*-dimethylcyclopropane (**1**).

CD effects of the cyclopropane chromophore have also been detected for gem-dimethylcyclopropanes which are attached *cis* to another ring, such as **116–120**[82].

For **116–120** having a cyclopropane chromophore of local symmetry C_s strong negative Cotton effects are detected between 200 nm (ε 1000) and 185 nm (ε 2930). The dichroitic absorptions $\Delta\varepsilon$ of the above alcohols have different orders of magnitude from those which are found for monofunctional hydroxy-steroids[82] or other alcohols[83]. Therefore, the main CD effect of **118–120** must come from the cyclopropane chromophore. As a summary one can say that conventional CD techniques (measuring solution spectra with commercially available instruments) is not yet very elaborated and informative with regard to deductions of absolute configurations of cyclopropane hydrocarbons or detections and assignments of electronic bands of the cyclopropane chromophore, respectively. CD is utilized only on a qualitative level.

Probably, the formation of 'cottonogenic derivatives' of cyclopropanes would be helpful in utilizing CD for the deductions of absolute configurations of cyclopropane hydro-



Compound	Substituent	$\Delta\varepsilon^a$	λ(nm)
116	None	−3.9	188
117	8-α Me	−5.1	193
118	8-α OH	−4.0	187
119	8-β OH	−3.8	195
120	8-α Me, 9-α OH	−5.9	197

[a] In *n*-hexane solution.

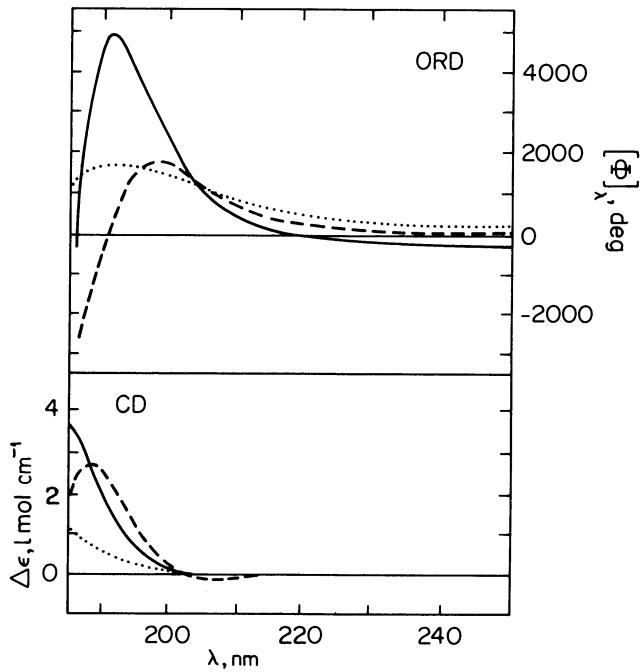
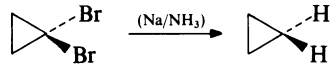


FIGURE 5. Optical rotatory dispersion (ORD) and circular dichroism of *trans*-disubstituted cyclopropane hydrocarbons ((**1**) (——); (**114**) (. . . .); (**115**) (- - - -))[81]. *Reprinted with permission from Moore* et al., J. Am. Chem. Soc., **93**, *4932, Copyright (1971) American Chemical Society*

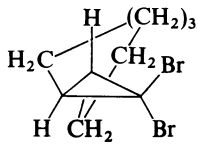
carbons. Such a method requires the introduction of substituents which, on the one hand, induce relatively strong Cotton effects at lower wavelengths. On the other hand, the corresponding low energy Cotton effect inducing ligands should be transferable rather easily into hydrogen atoms. One such kind of cottonogenic derivative of cyclopropane hydrocarbons would be the gem-dibromo compounds **XXII**. These halogenides can be



(XXII)

smoothly transformed into the hydrocarbons, for instance, via reduction with sodium in liquid ammonia.

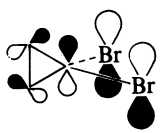
A particular example of a cottonogenic derivative is provided by (1*S*, 8*S*)-(+)-8,8-dibromo-*trans*-bicyclo[6.1.0]nonane (**121**) which can be transformed into **115**[81]. **121** (with a maximum optical purity of 72.5%) displays two rather strong, oppositely signed CD bands. Methylene bromide (CH_2Br_2) has its low energy electronic bands[84] at the same positions as does **121**.



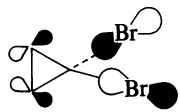
$\Delta\varepsilon(\lambda.\nu)$: −1.0 (221 nm, 45 250 cm^{-1})
+9.9 (191 nm, 52 360 cm^{-1})

(121)

The corresponding electronic transitions are assumed to originate with corresponding combinations of bromine (in-plane and out-of-plane) lone-pairs n_{Br} and to terminate at the C–Br antibonding σ orbital $\sigma^*_{C\text{-}Br}$. This orbital $\sigma^*_{C\text{-}Br}$ contains considerable contributions from bromine d-atomic orbitals[84]. In analogy to the orbital scheme of 1,1-dibromoethylene ($H_2C{=}CBr_2$)[85] and the orbital energies of cyclopropyl bromide[86] the CD bands of **121** should involve the $n_{Br}(b_2) \rightarrow \sigma^*_{C\text{-}Br}(a_1)$ and $n_{Br}(b_1) \rightarrow \sigma^*_{C\text{-}Br}(a_1)$ transitions, respectively. The occupied orbitals b_2 and b_1 result from interactions of the two components of the cyclopropane 3e′ orbital (Figure 4) with the bromine lone-pairs. In $n_{Br}(b_2)$ rather pronounced π-conjugative interactions occur.



$n_{Br}(b_2)$



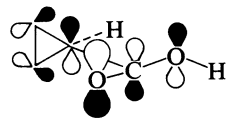
$n_{Br}(b_1)$

$\sigma^*_{C\text{-}Br}(a_1)$

B. Substituent Effects of the Cyclopropyl Group on the Circular Dichroism of Selected Chromophores

1. Carboxylic acids and acid derivatives

Cyclopropanecarboxylic acids and their derivatives generally achieve bisected conformations **VI** so that the π systems of the carboxy group and the A-component of the 3e′ orbital of **112** can interact conjugatively[19–21]. This type of interaction is depicted for the HOMO of a cyclopropanecarboxylic acid in **XXIII**. In the liquid phase mostly mixtures of *cis* and *trans* (**VIII**, **VI**) conformers of cyclopropanecarboxylic acids are found. In the parent compound, cyclopropanecarboxylic acid, the *cis* form seems to be preferred[17]. For substituted cyclopropanecarboxylic acids, however, different conformer populations may



(XXIII)

exist, for instance, involving also gauche forms. Cyclopropanecarboxylic acid or, for instance, (1*R*, 2*R*)-(−)-2-methylcyclopropanecarboxylic acid (**13**) exhibits a weak absorption ($\varepsilon \approx 100$) near 230 nm[87] which should correspond to the (n, π^*) transition[88]. The strong (π, π^*) transition will be found below 200 nm[88]. The absorption and CD spectra of **13**[87] are displayed in Figure 6.

13 has a rather weak (n, π^*) CE ($[\theta] \approx 4 \cdot 10^2$ at *ca.* 230 nm). For the deuterated cyclopropane amino acid **109** ($[\alpha]_D - 0.90°$ (H_2O)) a small CD is found at 205 nm[45]. This band corresponds obviously to 'band 1' of acyclic amino acids[88].

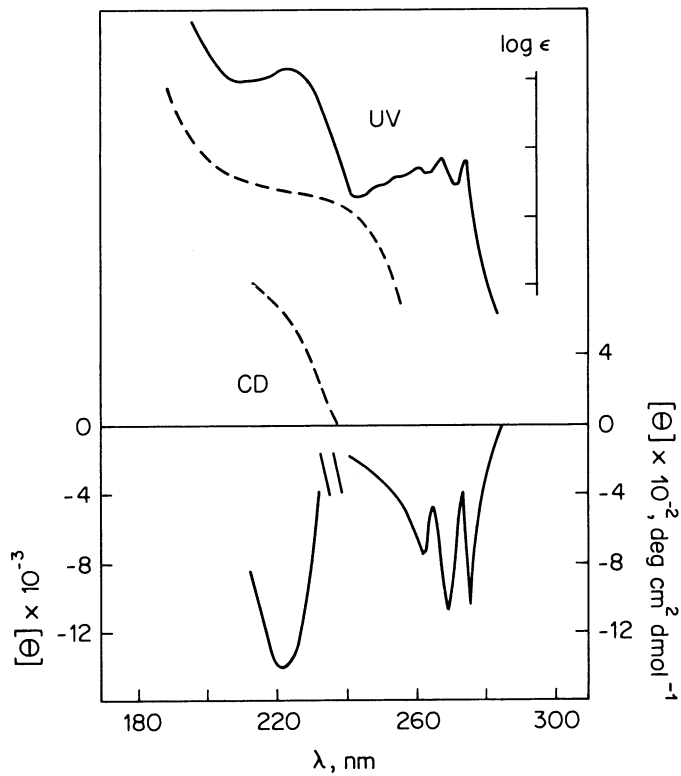
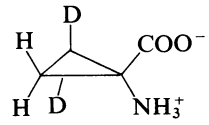


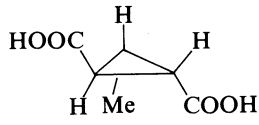
FIGURE 6. Absorption and CD spectra of (1*R*, 2*R*)-(−)-*trans*-1-methyl-2-phenylcyclopropane (**20**) (solid curves) and (1*R*, 2*R*)-(−)-*trans*-2-methylcyclopropanecarboxylic acid (**13**) (dashed curves) in methanol solution[87]. *Reprinted with permission from Verbit and Inouye*, J. Am. Chem. Soc., **89**, *5717, Copyright (1967) American Chemical Society*



$\Delta\varepsilon(\lambda)$: $+5.0 \times 10^{-3}$ (205 nm)

(109)

A rather strong CD signal is observed at 212 nm in the CD spectrum of the (1*S*, 2*S*)-(+)-cyclopropane dicarboxylic acid **122**[89] ($[\alpha]_D + 100°$ (EtOH)). The strong CD of **122**



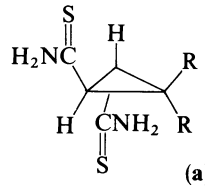
$\Delta\varepsilon(\lambda)$: -18(212 nm) in H_2O

(122)

probably does not result from a (n, π^*) transition. If in cyclopropanecarboxylic acid the (π, π^*) excitation has a transition moment which, in the preferred *cis* form, is polarized approximately along the C=O bond direction, the lowest energy (212 nm) band of **122** may result from the out-of-phase (**B**) combination of the two individual (π, π^*) transitions. The interaction in the B-mode will shift the (π, π^*) band to lower energy relative to the original position of the (π, π^*) excitation of a single carboxylic functionality.

(A) **(B)**

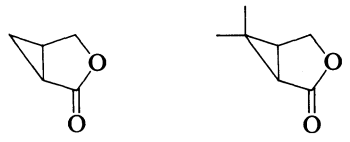
Determinations of absolute configurations of *trans*-cyclopropane-1,2-dicarboxylic acids on the basis of a definite Cotton effect seem to be possible for carboxylic acid thioamides. In these molecules, such as **123a** and **123b**, there is a Cotton effect near 330 nm which results from the (n, π^*) excitation of the thioamide chromophore[90]. In the



(123) **(a)** R = H **(b)** R = Me

	$[\alpha]_D$ (MeOH)	Extrema					UV	
		$[\Phi]_\lambda$	λ (nm)	$[\Phi]_\lambda$	λ (nm)	$[a] \times 10^{-2}$	λ (nm)	ε
123a	−906°	−14 700	351	−2260	341	−124	330	196
123b	+72°	−985	385	+6020	310	−70.1	330	160

thioamides **123a** and **123b** the rotation amplitude [a] reflects a negative Cotton effect for compounds of (R, R)-configurations[90]. Distinct CD bands from (n, π^*) transitions are found in lactones with a cyclopropyl moiety in α, β-position relative to the carbonyl moiety, such as the 3-oxabicyclo[3.1.0]hexan-2-ones **124** and **125**[91] (in MeOH). The



(124) **(125)**

$\Delta\varepsilon(\lambda)$: 0 (250 nm) $\Delta\varepsilon(\lambda)$: 0 (250 nm)
−6.77 (217 nm) −2.17 (218 nm)

negative signs for the (n, π^*) CD bands of **124** and **125** are in agreement with Weigang's lactone sector rule which is an octant rule with the sign pattern depicted in Figure 7[88].

In Figure 7 two views must be considered, one view along the OCO angle bisector and one from above. In Figure 7 the curved surface is a spherical distortion of the yz plane of the octant rule nodal plane (cf. also Subsection III.B.4). Other nodal surfaces remain planar. The signs refer to the back octants. Hence, the lactone rule is an octant rule with opposite signs.

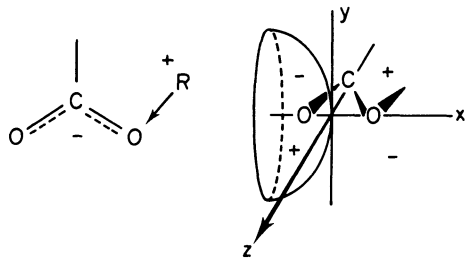
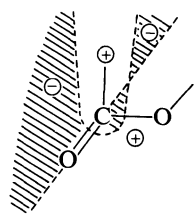


FIGURE 7. The sector rule of Weigang and coworkers for the lactone chromophore

The negative signs for the (n, π^*) CD bands of the lactones **124** and **125** follow also from Snatzke's lactone sector rule with the sign pattern for the upper sectors (above the plane of the paper) depicted below[88]. This last rule is based on the nodal surfaces of the n_y and π_3^*



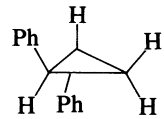
orbitals of the lactone (n, π^*) transition. The lactone orbitals are viewed as slightly modified COOH orbitals (in **XXIII** the HOMO π_2 is displayed; in π_3^* both the oxygen atoms have LCAO coefficients of equal signs and opposite to that of the carbonyl carbon atom).

2. *Phenylcyclopropanes*

In Figure 6 the CD spectrum of (1*R*, 2*R*)-(−)-*trans*-2-methyl-1-phenylcyclopropane (**20**) is displayed. At low energy **20** has a negative structured band with a weak CD ($\Delta\varepsilon \simeq -0.3$) between 260 and 280 nm. At 222 nm a moderately strong CD band with the same sign is observed ($\Delta\varepsilon \simeq -4.2$)[87]. (1*R*, 2*R*)-*trans*-2-phenylcyclopropane-1-carboxylic acid (**22**) exhibits a CD spectrum similar to that of **20**, except that the 222 nm CD is increased ($\Delta\varepsilon \simeq -6$)[87]. In the CD spectrum of **22** to the blue region of the 222 nm band a strong negative CD is observed.

It is clear that the 270 nm and 222 nm bands are associated with the $^1B_{2u}(^1L_b)$ and $^1B_{1u}(^1L_a)$ excited states of the phenylcyclopropane chromophore[87]. $^1B_{1u}$ results from an electric allowed transition. Owing to the conjugative interactions in the bisected conformations of the phenylcyclopropanes[21] these last bands are found at lower energies than the corresponding bands in benzene.

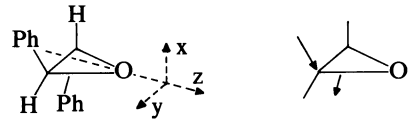
It has been proposed that a negative sign of the $^1B_{1u}(^1L_a)$ CD band is characteristic for a phenyl group attached to a cyclopropane carbon atom of the *R*-configuration of a *trans*-substituted cyclopropane derivative[87]. This rule is also true for (1*R*, 2*R*)-(−)-1,2-diphenylcyclopropane (**19**)[15b] ($[\Phi]_D - 790.8°$ ($CHCl_3$)). The high energy CD exhibits a marked solvent effect ($\Delta\varepsilon(\lambda)$: −19.7 (235 nm) in $CHCl_3$)[15b].



(**19**)

λ (nm)	Δε (in *n*-hexane)
276	−4.40
268	−5.30
262	−3.94
230	−29.7

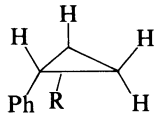
In terms of exciton theory which is developed quantitatively for (−)-*trans*-stilbene oxide (**126**)[92] the 230 nm band results from the out-of-phase combination of the electric allowed B_{1u} state transition moments. The B_{1u} state has a transition moment which is polarized



(**126**)

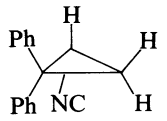
(approximately) along the single bond linking the phenyl and cyclopropane moieties. That the resultant B transition in **19** is shifted to lower energy (230 nm) as compared to B_{1u} in **20** (222 nm) follows from consideration of the Coulombic interactions of the two individual (B_{1u}) transition moments. In the B combination attractive forces operate whereas in the A combination there is repulsion. The out-of-phase coupling of the two monomer excitation moments of **19** entails a left-handed helical charge displacement along and around the *X*-axis, giving rise to a negative Cotton effect.

In contrast to the *trans*-disubstituted phenylcyclopropanes *cis*-disubstituted phenylcyclopropanes, such as **23** and **30**, do not show any detectable CD signals[15a]. This is reasonable, if the optical activity of the two lowest energy electronic bands of phenylcyclopropanes are generated essentially by the coupled-oscillator mechanism[1] (exciton mechanism for the degenerate case, such as **19**). In *cis*-phenylcyclopropanes the interacting transition moments will lie (approximately) in the same plane. Hence, in the coupled-oscillator mechanism there will be only a very small Cotton effect (which is zero, if



23 R = COOH
30 R = CH_2OH

the excitation moments lie exactly in the same plane). Using the findings on the CD of *trans*- and *cis*-phenylcyclopropanes the CD of (*R*)-(−)-2,2-diphenylcyclopropyl isocyanide (**36**)[36] (in methanol) can be understood qualitatively. Due to steric interactions in



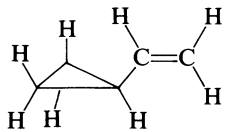
(**36**)

λ (nm)	Δε	λ (nm)	Δε
350	−0.0088	255	−0.4554
275	−0.0044	250	−0.3167
269	−0.5256	240	−0.1927
265	−0.4290	234	−0.3416
261	−0.5692	232	−0.2365

36 the two phenyl groups will probably not achieve the preferred bisected conformations. This may be the reason for the decrease of the magnitude of the Cotton effect of **36** in comparison with those of **20** and **22**. If the two phenyl groups are viewed as (approximately) independent subsystems, the *cis*-Ph/NC couple will not contribute to the 230 nm (B_{1u}) Cotton effect. On the other hand, the *trans*-Ph/NC couple shall induce a negative Cotton effect at ca. 230 nm, as is observed experimentally.

3. Vinylcyclopropanes

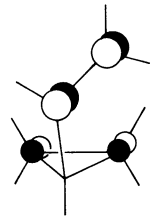
The vinylcyclopropane chromophore takes an exceptional position among the compounds in which a double bonded group is linked to the cyclopropane ring. In the parent molecule, vinylcyclopropane (**127**), there is a s-*trans*-gauche conformational equilibrium[93, 94], whereas in all other related double bonded compounds (acids, aldehydes, etc.) s-*trans* and s-*cis* conformers are preferred[17, 94].



(**127**)

Referring to the orbital diagram of cyclopropane (**112**) (Figure 4) it is clear that in bisected conformations (s-*cis* ($\omega = 0°$) and s-*trans* ($\omega = 180°$)) only the A-components of the 3e′ and 4e′ orbitals of **112** can interact mesomerically optimal with the π and π^* orbitals of the ethylenic moiety. Hence, in a simplified model the frontier orbitals $\varphi_{(i)}$ of **127** may be described as given below (neglecting LCAO coefficients). On the other hand, in a 'perpendicular' conformation (**127-p**) the S-components of 3e′ and 4e′ will preferentially interact with the double bond orbitals π and π^* to give the resulting orbitals $\psi_{(i)}$.

For 'intermediate' (gauche) conformations or otherwise perturbed systems the frontier orbitals ($\bar{\pi}$ and $\bar{\pi}^*$) can be described as a mixture of the corresponding orbitals $\varphi_{(i)}$ and $\psi_{(i)}$. For the cyclopropane subunit the φ/ψ mixtures are shown qualitatively in Figure 8[95].



$\varphi_{(1)} \approx \pi - 3e'$ (A)
$\varphi^*_{(1)} \approx \pi^* + 4e'$ (A)
$\psi_{(1)} \approx \pi - 3e'$ (S)
$\psi^*_{(1)} \approx \pi^* + 4e'$ (S)

(127-p)

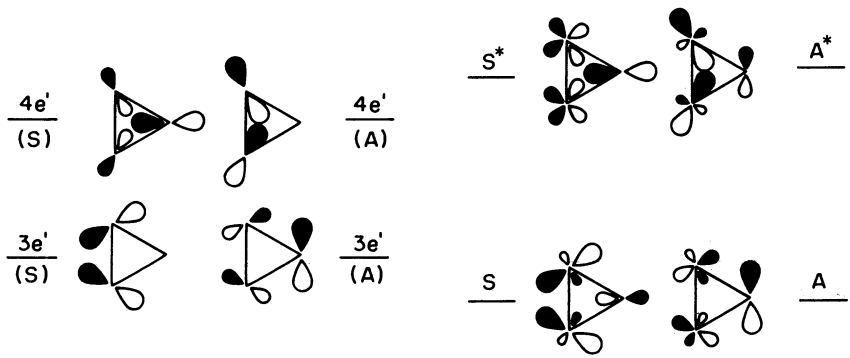
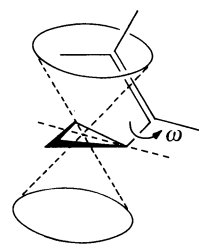


FIGURE 8. Cyclopropane frontier orbitals in substituted compounds. Left: Walsh orbitals. Right: MOs after allowing for ca. 20% mixing between the 3e′ and 4e′ orbitals (the resulting orbitals being denoted as S, A, S*, A*)[95]. *Reproduced by permission of The Weizmann Science Press of Israel*

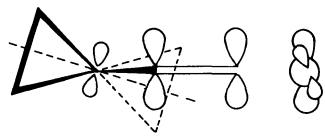
For substituted cyclopropanes it has turned out that HOMO–LUMO interactions may also occur. However, a crude description of the frontier orbitals of the vinylcyclopropane chromophore seems to suffice for a treatment of chiroptical properties[95]. This description takes only mixtures of occupied or unoccupied orbitals φ and ψ into account. Other things being equal, the A and S* interactions with π and π^*, respectively, will be larger than those of S and A* owing to the greater MO coefficients on the cyclopropane carbon atom connected with the double bond. With respect to the dihedral angle ω characterizing the relative orientations of the cyclopropane and ethylenic subunits one can define three regions with different descriptions of the HOMO → LUMO excitations which influence the CD decisively.



Region	ω (deg)	Relevant HOMO → LUMO excitation ($\bar{\pi}, \bar{\pi}^*$)
I	$0 \leqslant \omega \leqslant +20$	$(\pi - A) \rightarrow (\pi^* + A^*)$
II	$+20 < \omega \leqslant +70$	$(\pi - A) \rightarrow (\pi^* + S^*)$
III	$+70 < \omega \leqslant +90$	$(\pi - S) \rightarrow (\pi^* + S^*)$

The HOMO–LUMO excitation ($\bar{\pi}, \bar{\pi}^*$) of vinylcyclopropanes gives rise to a strong electronic band near 210 nm[95]. If the cyclopropane ring or the double bond (or both) are substituted by alkyl groups, the lowest energy Cotton effect will be observed near 225 nm[95].

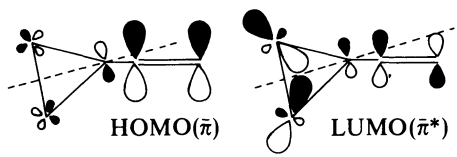
In chiral vinylcyclopropanes the chromophore can be viewed as inherently chiral, i.e. all the electronic transitions have simultaneously an electric (μ) and a magnetic (m) transition moment. For transoid or cisoid (indicated in broken lines below) arrangements the magnetic moments are generated by a circular displacement of electric charge density around the bond between the cyclopropane and the ethylenic moieties. The helical movement of electron density involves essentially p-atomic orbitals twisted relative to each



other. With the above crude model Snatzke and coworkers[95, 98] could rationalize the sign pattern for the CD of vinylcyclopropanes with the dihedral angles ω. The results (for all the different regions $-180 \leqslant \omega \leqslant +180°$) are summarized in Figure 9[95].

There are two main points in the helicity sector rule of vinylcyclopropanes. First, the dihedral regions I and II ($0 \leqslant \omega \leqslant +20$; $+20 < \omega \leqslant 70°$) will develop the same signs for the Cotton effect of the first strong electronic band. Second, the sign pattern alternates with increasing dihedral angle according to plus ($0 \leqslant \omega \leqslant +70°$), minus ($+70 < \omega \leqslant 90°$), plus ($+90 < \omega \leqslant +110°$), minus ($+110 < \omega \leqslant +180°$). For negative dihedral angles this sign pattern is reversed.

The deduction of the above results will be illustrated for a special case. For instance, for negative torsional angles the sign of the CD within area I for a transoid ($\omega = +165°$) vinylcyclopropane is derived from the determinations of the angle between the electric (μ) and magnetic (m) transition moments developed during the HOMO → LUMO excitation. The HOMO → LUMO excitation gives a charge density distribution Q (excitation multipoles) which are obtained formally from multiplication of the LCAO coefficients of corresponding atoms of the HOMO and LUMO and subsequent sign inversion (to



account for the negative electronic charge). Linear charge density displacement between the charged atoms generates the electric transition moment μ from two local electric moments μ_1 and μ_2. The circular charge density movement (indicated below by curved arrows) generates magnetic moments. For the HOMO → LUMO excitation the magnetic

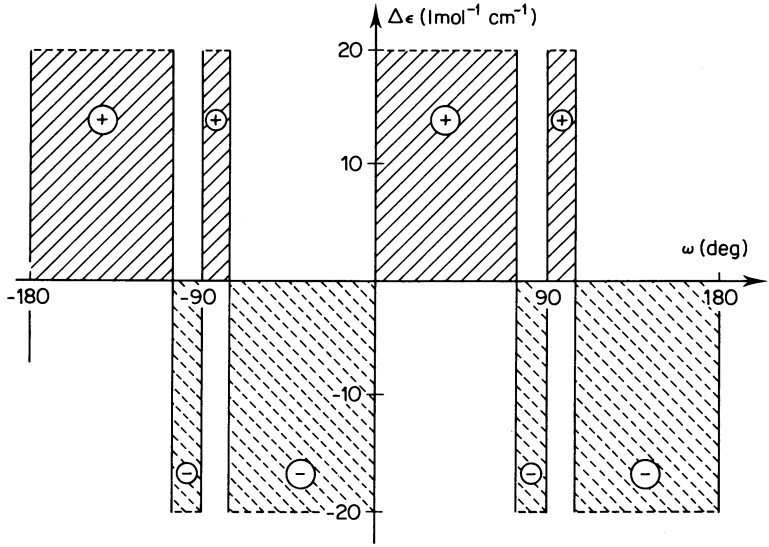
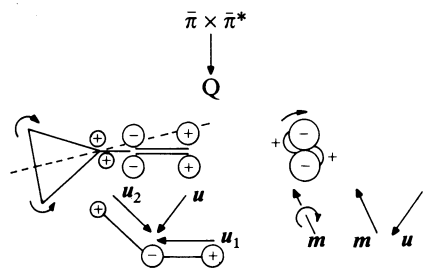


FIGURE 9. Graphical representation of the helicity rule for inherently chiral vinylcyclopropanes[95]. *Reproduced by permission of The Weizmann Science Press of Israel*

moments induced in the ring will cancel. Therefore, the only significant magnetic moment will be induced in the distorted three-center π system which is reminiscent of the allyl anion



(or the isoelectronic enol ether)[96]. The magnetic moment $\boldsymbol{m}$ is determined by the inherent charge density rotation during the charge translation along the direction of the electric moment μ_2. Hence, for the negative torsional angle chosen the angle between μ and $\boldsymbol{m}$ is obtuse and the CD in region I should be negative. CD data for some selected vinylcyclopropane derivatives are summarized in Table 7[95].

4. *Cyclopropyl ketones and aldehydes*

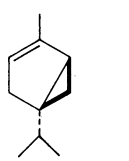
a. Octant and antioctant behavior of cyclopropyl ketones

Optical activity of cyclic ketones has played a key role in the (theoretical and experimental) advancement of utilizing chiroptical properties for stereochemical purposes.

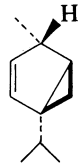
TABLE 7. CD data of selected vinylcyclopropanes[95]

Compound	ω (deg)	Solvent[a]	$\Delta\varepsilon$ (l mol^{-1} cm^{-1})	λ_{max} (nm)
128	−30	M	−14.5	200
		O	−11.5	205
129	+30	M	+7.1	200
		O	+9.5	205
102	+60	M	+5.0!	210
		O	+6.0!	215
100-t	+60	M	[a] = +11800[b]	—
130	+150	M	−12.4	207
		C	−11.9	207
			+7.3	185
131	−150	M	+19.6	213
		O	+18.5	210
132	+150	M	−4.6	215
		O	−5.1	214
133	−110	M	+4.5	227
	(−120)	O	+9.1	226
			−21.4	203
134	−130	M	+5.1	228
			−11.9	205
		O	+8.2	225
			−14.9	205

[a] C, cyclohexane; O, isooctane; M, methanol.
[b] ORD of **100-t**, [a] being the Cotton effect amplitude.



(128)



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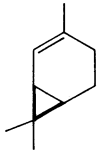
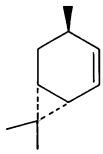
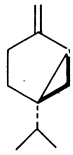


(102)



(100-t)



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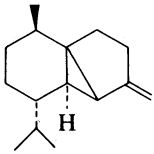

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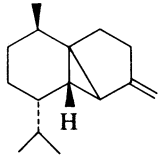
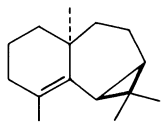


(132)



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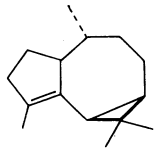


(134)

Here, in particular, the Cotton effect (CE) of the (n, π^*) band of carbonyl compounds (around 280 nm) was of central importance[1]. For the establishment of the relationship between molecular structure (conformation) and the (n, π^*) CE several rules with various theoretical backgrounds (and various levels of sophistication) are available[1, 97].

On the lowest level the carbonyl chromophore is viewed as the prototype of an 'inherently symmetric, but chirally perturbed chromophore'[1]. This means that in a chiral ketone the particular carbonyl chromophore retains (largely) its (achiral) symmetry and optical activity will be induced by the chiral environment (i.e. the chiral arrangement of other groups in the whole molecule). In terms of perturbation theory this can be expressed by the statement that in zeroth order the chromophore is achiral and chirality is induced by perturbations in first (or higher) order. On the other hand, if, for a given electronic excitation, optical activity exists in zeroth order (without perturbation by the chiral field of the remaining groups of the molecule not directly involved in the electronic transition) the chromophore is termed 'inherently chiral'[1].

On the lowest level, using symmetry and nodal properties of the MOs of $H_2C{=}O$ as a representative of the inherently symmetric carbonyl chromophore, an 'octant rule' can be derived for the influence of a (static) perturber of the (n, π^*) excitation[1]. The geometrical symmetry (C_{2v}) of the $H_2C{=}O$ unit with the two symmetry planes, yz and xz, leads to a quadrant rule. If the orbitals involved in the (n, π^*) excitation of ketones are described as $n = 2p_O^y$ and $\pi^* = N \cdot (2p_O^x - 2p_C^x)$ (N being a normalization constant), the nodal plane (xy) of the virtual orbital generates the octant diagram for the contributions of substituents of chirally perturbed compounds (Figure 10).

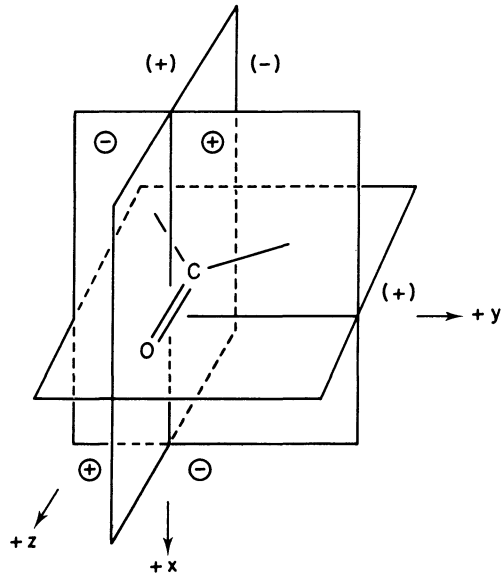
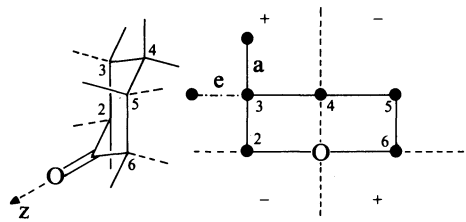


FIGURE 10. The lowest level octant diagram for the contributions of substituents of chirally substituted carbonyl compounds to the (n, π^*) Cotton effect (the carbon and oxygen atoms and the sp^2 single bonds lie in the yz plane. Front and back octants are separated by the xy plane which goes through the center of the C=O bond)

From empirical observations it was deduced that the (positive or negative) contributions of incompletely shielded carbons (H, C moieties) may be fixed, if the oxygen atom is in the $+z$ direction with respect to the carbonyl carbon and the observer looks from the $+z$ direction toward the oxygen (Figure 10). Hence, the sign of the contribution to the optical activity of a carbonyl (n, π^*) band which a given atom (or group) at point (x, y, z) makes to the Cotton effect will vary as the product $x \cdot y \cdot z$ of its coordinates.

In this model the front and rear octants are separated by the xy plane which goes through the center of the C=O bond.

Modifications of this simple model may be introduced, if one takes into consideration that the C=O π^* orbital will not have its node halfway between the carbon and oxygen atom ($\pi^* = N \cdot (2p_O^x - \lambda \cdot 2p_C^x)$ and $\lambda \neq 1$). Applying the octant rule one finds that, for instance, in (+)-3-methylcyclohexanone in the chair form the ring carbons 2, 4, 6 lie on nodal octant planes. Carbon atoms 3 and 5 make equal positive and negative contributions and, hence, will cancel. Only the methyl group (attached to ring carbon 3) generates a positive contribution which is not balanced by any corresponding negative one. This is true for the methyl group achieving an equatorial (e) or axial (a) arrangement, respectively.



From the very beginning the octant rule ran into difficulties because several (mostly well-defined) observations did not agree with its predictions. Striking examples where the octant rule is in serious conflict with the observations for a whole class of compounds are provided by the 'conjugated' (α, β)-cyclopropyl ketones. Here, the predicted signs of the (n, π^*) CE were often opposite to the experimental findings. Therefore, for these types of molecules as an empirical finding an 'antioctant rule' was assumed to be applicable.

In order to rationalize the particular situation of the optical activity of cyclopropyl ketones (i.e. to rationalize the influence of a cyclopropane ring on the carbonyl optical activity) two fundamentally different approaches can be followed. First, one may cling to the octant rule. Then, as conformations resulting in different relative arrangements of the cyclopropane and carbonyl moieties play an important sign determining role, one takes conformational changes or preferences, respectively, explicitly into consideration. For instance, a chair conformation of a particular six-membered ring may be changed by the introduction of a cyclopropyl ring into a half-chair or boat conformation. Another approach retaining the essential foundations of the octant rule takes into consideration that in complex carbonyl compounds the π^* orbital does not have a nodal plane, but rather a curved surface, for instance, running back from the $+z$ direction after it crosses the C=O bond[1a].

A second approach to rationalize 'reversed' octant (or irregular) behavior of cyclopropyl ketones is to include delocalization (conjugation) effects of the n and π^* orbitals. This means that, for certain geometrical situations, the carbonyl chromophore is extended to become an inherently chiral chromophore. The signs and magnitudes of the Cotton effects of inherently chiral chromophores will vary strongly with the relative orientations of the conjugatively interacting subunits. The successful treatment of the (n, π^*) optical activity of cyclopropyl ketones, hence, depends critically on the recognition of those relative orientations of the cyclopropane and carbonyl moieties from which one can infer whether

both these subunits interact weakly (inherently symmetric chromophore) or strongly (inherently chiral chromophore). This is important as this treatment of the cyclopropyl ketone optical activity requires for the interpretation of the CE, in general, the consideration of the relative weights of the CE contributions from the inherently chiral chromophore and contributions following from the octant rule.

A special model for rationalizing the (n, π^*) optical activity of the cyclopropyl ketones is that suggested by Snatzke[97]. It is a truncation of the last mentioned method in that it takes only the contribution from the inherently chiral chromophore into account. In the Snatzke treatment there are two basic requirements. First, the carbonyl group and the cyclopropane ring must not achieve a bisected, but a gauche arrangement. Second, significant electron delocalization is not only considered for the π^* orbital, but also for the n orbital. In the Snatzke model the delocalization of the n orbital is achieved through mixing of n with the π HOMO of the cyclopropyl ketone to give a resulting (extended) n' orbital. This n' orbital contains a $2p_O^y$AO plus an admixture from an orbital corresponding to $\varphi_{(1)}$ of vinylcyclopropanes (Figure 8). In this way, the magnetic allowed (n', π^*) excitation gains a non-zero electric transition moment from an admixture of the (π, π^*) transition into (n, π^*). Figure 11 illustrates how a negative (n', π^*) Cotton effect is generated by (almost) antiparallel electric (μ) and magnetic (**m**) transition moments in chiral cyclopropyl ketones of conformation **XXIV**. For a given sign pattern of the π HOMO in the mixed orbital n' the phase of $2p_O^y$ is determined by the phase of the 2p AO at the atom C-α[97]. In the Snatzke model the effect of chirality of the compounds is a truncation of mixing (close lying) frontier orbitals of the subunits of the compounds. In a more general approach the $\langle n, \pi^* \rangle$ excited state in first order will be expanded into a series of (zeroth order) excited states wavefunctions, for instance, according to equation 22.

$$\langle n, \pi^* \rangle = (n, \pi^*) + \sum_i b_i \cdot (3e', 4e')_i + \ldots + CT \tag{22}$$

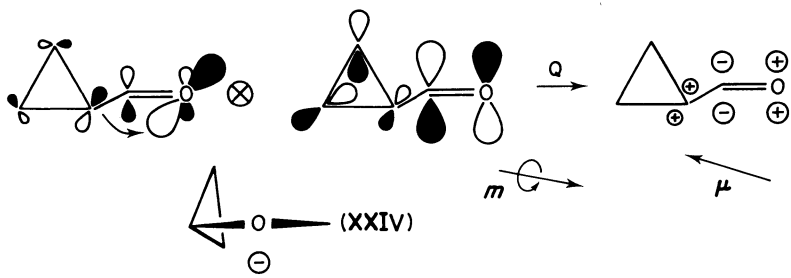


FIGURE 11. The Snatzke helicity rule for the (n, π^*) Cotton effect of inherently chiral cyclopropyl ketones

In the expansion 22 the expressions in parentheses represent zeroth-order excitations localized at the carbonyl or cyclopropane moieties, respectively. The term CT includes charge-transfer components and depends upon the extent of mesomeric interactions between the subunits. The sum in equation 22 is over all the HOMO → LUMO (3e', 4e') transitions of cyclopropane (cf. Subsection III.A). Actually, of course, more excitations have to be included into expansion 22. In particular, expansion 22 does not include Rydberg excitations.

In contrast to the Snatzke approach where mixing is achieved on the orbital level the last approach concentrates on mixing on the excited states' level.

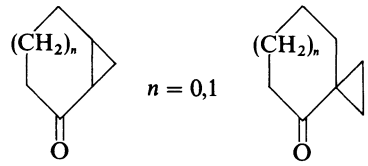
For flexible molecules application of one or the other above-mentioned approaches to optical activity of cyclopropyl ketones implies an often delicate analysis of conformer populations to find the most stable conformer. On the other hand, it is by no means clear whether the preferred conformation also provides the strongest CE. It may well be that a less abundant conformer contributes the strongest CE so that its CE determines the sign of the overall observable CD. Conformer equilibria are generally investigated through observations of temperature effects on the CD (or other physical properties). When discussing temperature dependence of CD, however, it is often very difficult to separate effects of conformational and solvational equilibria. The solvational equilibria result from the presence of solvated and unsolvated (or differently solvated, respectively) species with sometimes oppositely signed rotational strengths.

b. Cyclic compounds with an α, β-cyclopropyl ketone chromophore

Cyclopropyl ketones with the cyclopropane and carbonyl moieties in the α, β-position have their (n, π^*) bands between 280 nm and 310 nm. For these compounds, additionally, the (π, π^*) Cotton effect can be observed between 200 nm and 215 nm. As usual the position of the (n, π^*) band will shift to lower energy, if a hydrocarbon solvent is changed into an alcohol. The (π, π^*) band shows the reversed solvent effect.

The above discussions about octant and antioctant behavior of cyclopropyl ketones has revealed that often there exists ambiguities in the interpretation of the CD spectra of these compounds. Therefore, sometimes the discussions of CD spectra of cyclopropyl ketones are a posteriori explanations of the experimental findings rather than a priori predictions of the outcomes of the experiments. This means that, in particular, the antioctant rule is viewed as a regularity and discrepancies have to be explained in terms of deviations from the foundations of that rule (such as conformer populations and/or special electronic situations of the chromophore).

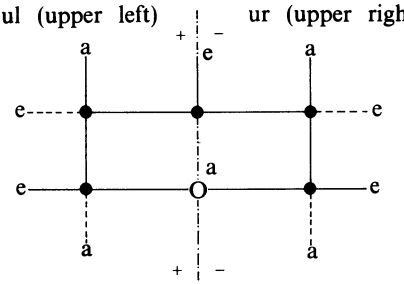
For geometrically rather well defined situations for the application of the antioctant rule two basic situations are differentiated, namely condensed systems (fused rings) **XXV** and spiro-compounds **XXVI**[99]. The geometrical arrangements in these systems can be defined

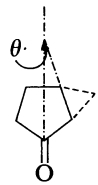


(XXV) **(XXVI)**

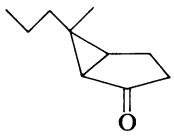
through the angle θ between the plane of the three-membered ring and the xz plane of the carbonyl group and through the torsion angle τ for $O\text{–}C_1\text{–}C_2\text{–}C_3$. Generally, the cyclopropane ring (denoted as Δ) will be in the back octants, with the sign pattern for alkyl groups given below for the 'normal' octant rule (cf. also Figure 10). In this way, for the bicyclo[3.1.0] pattern of **135** and **136**[100] the inverse octant rule leads to the prediction of negative (**135**) and positive (**136**) (n, π^*) Cotton effects, respectively (cf. also the related lactones **124** and **125**). Similarly, antioctant behavior is found for **137**, **138**[99] and **139**[101]. More examples of this kind will be found in Refs 99 and 100.

All these data are also in agreement with the Snatzke model of the (n, π^*) CE of such compounds (Figure 11).



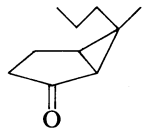


$\theta = 180°$
$\tau = 180°$
Δ in lr
CE < 0



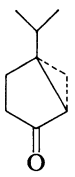
(135)

$[\Phi]_D + 10.6°$
CE < 0



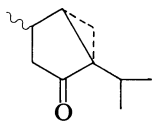
(136)

$[\Phi]_D - 11.4°$
CE > 0 at 292 nm



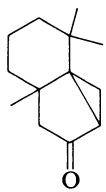
(137)

Δ in lr
$[a] - 20\,500°$ (MeOH)



(138)

Δ in lr
$[a] - 9300°$ (MeOH)



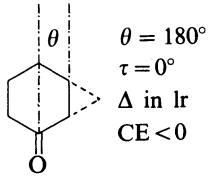
(139)

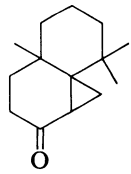
Δ in ur

$\Delta\varepsilon(\lambda)$: + 6.09(283); − 7.64(206) in methanol
$\Delta\varepsilon(\lambda)$: + 3.73(289); − 6.82(198) in isooctane

For the bicyclo[4.1.0]-type of cyclopropyl ketones compounds **140** and **141**, for instance, present support for the antioctant rule[101,102].

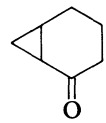
For the discussion of the relationship between the sign of the (n, π^*) Cotton effect and molecular structure of spiran-type cyclopropyl ketones, such as 3α,5-cyclo-5α-cholestan-6-one (**142**), one must consider that the perturbing group comes into the near lower left (nll) octant. Then, the reversed octant rule predicts a negative sign for the (n, π^*) CE which is





(140)[101]

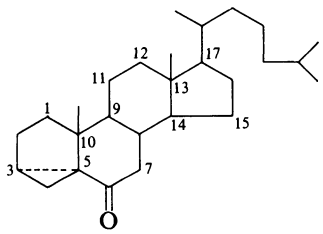
Δ in ur

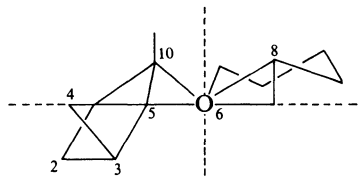


(141)[102]

Δ in ul
CE < 0

Δε(λ): +4.04(287); −8.97(209)
in methanol
Δε(λ): +3.52(299); −8.18(204!)
in isooctane



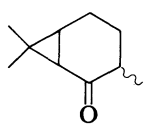


(142)

Δ in nll
[a] −4500°(dioxane)

found experimentally[99]. More data for compounds with a cyclopropane ring spiro to the carbonyl-carrying ring are given in Ref. 99.

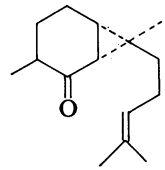
Apparent abnormalities from the antioctant behavior are observed for (+)-carone **(143)**[99] ([a] +4300°)[99]. The discrepancy for **143** has been explained by strong contri-



(143)

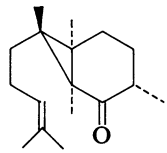
Δ in ul
[a] +5900°(MeOH)

butions of the geminal methyl groups to the (n, π^*) CE, i.e. the normal octant rule contribution (+) of the gem-dimethyl moiety overweighs the reversed octant contribution of the cyclopropane subunit. This explanation is apparently supported by the results for **141** where the gem-dimethyl moiety is absent and the compound exhibits the expected antioctant behavior. Corresponding effects as for **143** are found, for instance, for **144**[101,103], **145**[103] and **146**[103].

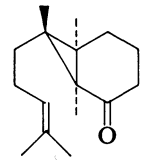


(144)

$\Delta\varepsilon(\lambda)$: + 2.20(287); + 3.03(217) in methanol[101]



Δ in ul



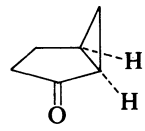
(145)

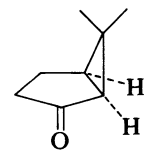
CE > 0 at 287 nm and 217 nm

(146)

$\Delta\varepsilon(\lambda)$: + 2.75(287); + 3.34(214) in methanol

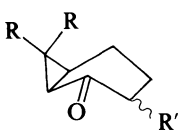
A situation similar to that of the pair **141** and **143** with respect to octant or anti-octant behavior, respectively, can be expected for the (structurally rigid) (2*R*)-bicyclo[3.1.0]hexan-2-one (**147**) and (2*S*)-6,6-dimethylbicyclo[3.1.0]hexan-2-one (**148**). Contrary to the pair **141** and **143**, however, both compounds **147** and **148** show antioctant behavior with positive (n, π^*) Cotton effects ($\Delta\varepsilon_{298}$ + 1.83 (**147**); $\Delta\varepsilon_{307}$ + 1.35

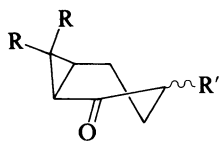


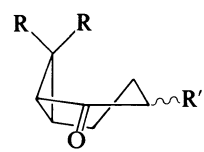


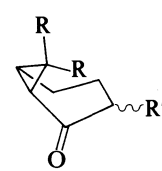
(147) **(148)**

(**148**))[104] (Figure 12). Based on this observation Lightner and Jackman[104] suggested that the addition of the gem-dimethyl moiety is insufficient to explain the (n, π^*) CE sign differences of **141** and **143** simply in terms of methyl group contributions to the CE sign according to the octant rule. Instead, they suggested that the difference in the CE signs of **141** and **143** are due to conformational differences imposed by the presence of the gem-dimethyl moiety (which cannot arise in the rigid compounds **147** and **148**). Generally, for **141** and **143** one can envisage boat (**XXVII**, **XXX**) and twist (**XXVIII**, **XXIX**) conformers. The octant rule predicts a (+) CE for each conformer. Considering the α, β-cyclopropyl ketones as inherently chiral chromophores one finds that the orbital angular relationships for the twist conformations, **XXVIII** and **XXIX**, are essentially identical, as given below.









(XXVII) **(XXVIII)** **(XXIX)** **(XXX)**

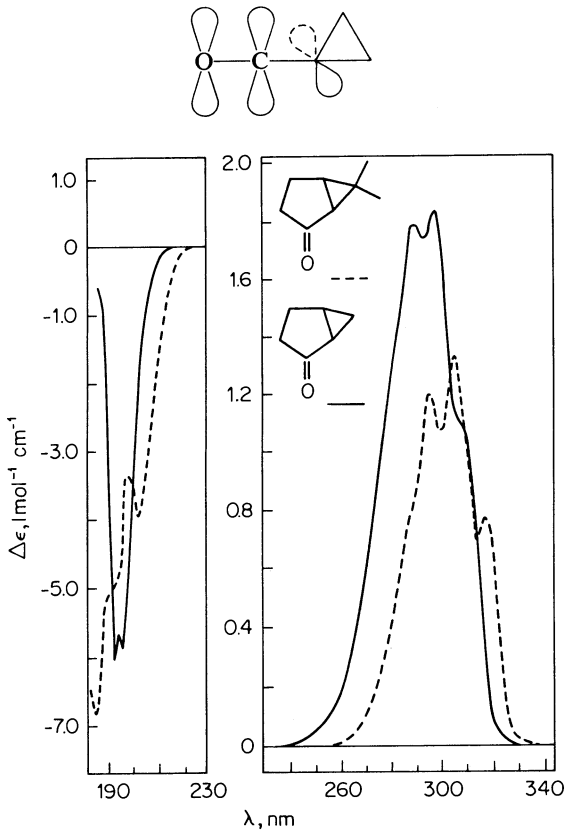


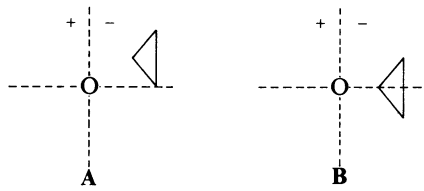
FIGURE 12. CD spectra of (2*R*)-bicyclo [3.1.0]hexan-2-one (**147**) and (2*S*)-6,6-dimethylbicyclo [3.1.0]hexan-2-one (**148**) in isopentane[104]. *Reprinted with permission of Pergamon Press from Lightner and Jackman*, Tetrahedron Lett., **1975**, *3051*.

The orbital relationships for **XXVIII** and **XXIX** are close to those for the geometrically rigid compounds **147** and **148**. However, **147** and **148** provide mirror images of the chromophores of **XXVIII** and **XXIX**. Hence, it was suggested[104] that in order for **141** to have a (−) (n, π^*) CE the relevant conformations of **141** should correspond to **XXVIII** and **XXIX**. Due to unfavorable non-bonded interactions in **XXIX** the preferred conformation of **141** must be **XXVIII**[104].

As (+)-carvone (**143**) has the same absolute arrangement of the carbonyl and cyclopropyl moieties as **141**, but opposite (n, π^*) CE, **XXVIII** has been ruled out as a conformational representative of **143**[104]. For **143** with the gem-dimethyl moiety steric interactions will be severe in the conformations **XXIX** and (especially) **XXX**. **XXVII** is assumed to be the most favorable representation of **143**. In **XXVII** the carbonyl π and cyclopropane p orbitals are almost orthogonal. Hence, there will be no contributions from an inherently chiral chromophore and the observed (n, π^*) CE can be rationalized by the sum of the normal octant-like contributions of the C(6)methyl and gem-dimethyl group[104]. In **XXVII** all components of the gem-dimethyl group lie nominally in a (+) back

octant. The configuration of the C(6)Me group (and, hence, its octant contribution), however, is uncertain.

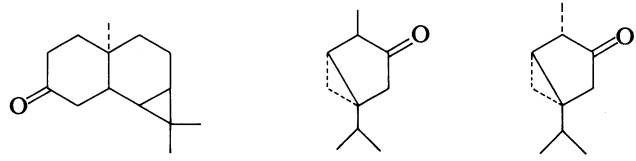
Apart from the (n, π^*) Cotton effect for the cyclopropyl ketones also the (π, π^*) CE can be utilized for the deductions of (absolute) molecular conformations. It has been suggested that there exists a correlation between the sign of the (π, π^*) CE and the molecular structure in a way which is formally dictated by the normal octant rule[101] (Figure 10). Accordingly, **139**, **140**, **144–148** should exhibit negative (π, π^*) CEs (**139**, **140**, **147**, **148**) or positive (π, π^*) CEs (**144–146**), respectively. This, indeed, is observed[101,103,104]. Kuriyama and co-workers' proposal[101] corresponds essentially to an empirical quandrant rule. Here, the cyclopropane ring as a perturber is either in one quadrant (A) or is spread over two quadrants (B). The former conformation A would result in a larger $\Delta\varepsilon$ value than B. A



theoretically more stringent approach to the relationships between the (π, π^*) CE and molecular structure of cyclopropyl ketones probably should be based on the Snatzke model[95,97] following the elaborations for the (π, π^*) CD bands of vinylcyclopropanes (Subsection III.B.3).

c. Non-conjugated cyclic cyclopropyl ketones

Cyclopropane rings which are not conjugated with a carbonyl moiety make no special contribution to the (n, π^*) CE[99]. Hence, the octant rule can be applied. This is demonstrated by the data for the (n, π^*) CEs of nor-maalione (**149**), (–)-thujone (**150**), and (+)-isothujone (**151**) in methanol as the solvent[99].

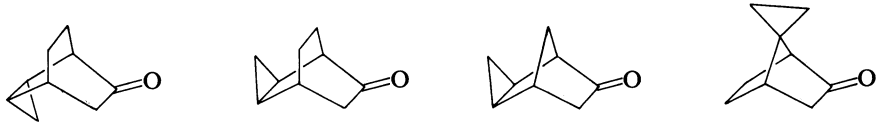


(149) $[a]+8400°$

(150) $[a]+2300°$

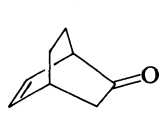
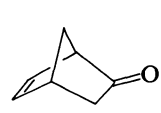
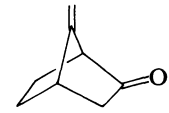
(151) $[a]+400°$

On the other hand, the situation becomes complex, if the cyclopropyl moiety bears a β,γ-relationship to the carbonyl group as in **152–155**[105]. Remembering the analogy of the



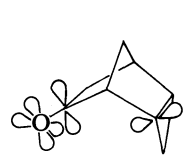
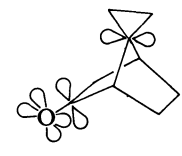
(152) **(153)** **(154)** **(155)**

cyclopropane ring and a C=C double bond it is clear that the last compounds should exhibit similarities with **156–158**.

(156) **(157)** **(158)**

In **156–158** homoconjugation effects are operative whose strengths depend decisively on the orientations of the interacting moieties. This is well known from photoelectron spectroscopy[107] and also UV absorption spectroscopy[106]. The increase of the (n, π^*) absorption intensity of **157** (ε 290), for instance, is discussed in Ref. 106. There it is shown that in the functionality $C_d{=}C_c{-}C{-}C_b{=}O_a$ there is considerable overlap (through space) between the atoms b and c, but also between the oxygen lone-pair and the C_c p-AO of the double bond. The type of homoconjugation is similar in **152–154** and **156**, **157** and can be represented schematically by **XXXI**.

(XXXI) **(XXXII)**

A different type of homoconjugation is found for the couple **155** and **158**. It is visualized by **XXXII**. Therefore, the treatment of these compounds under the subheading 'non-conjugated cyclopropyl ketones' is only justified by the formal criterion that the carbonyl and cyclopropane moieties are not in α, β-position.

In quantum theory the quantity characterizing the Cotton effect of a given electronic transition $0 \rightarrow i$ is the rotatory strength R_{0i}[1]. It corresponds to the scalar product of the electric (μ_{0i}) and magnetic (m_{0i}) transition moments of that excitation[1, 108].

$$R_{0i} = Im \langle 0 | \boldsymbol{m} | i \rangle \cdot \langle i | \mu | 0 \rangle = \boldsymbol{m}_{0i} \cdot \mu_{0i} \tag{23}$$

In equation 23 *Im* means to take the imaginary part of the corresponding expression. In a series of related compounds for a particular magnetic dipole transition, as is the (n, π^*) excitation of **152–154**, **156**, **157**, the magnetic transition moment is approximately constant, but the electric transition moment may vary widely. Then, if θ represents the angle between the directions of the electric and magnetic transition moments, an equation (24) exists ($|\mu_{0i}| \sim \sqrt{\varepsilon_{0i}}$).

$$\Delta\varepsilon_{0i} = \boldsymbol{m}_{0i} \cdot \cos\theta \cdot \sqrt{\varepsilon_{0i}} \tag{24}$$

This means that the dichroitic absorption $\Delta\varepsilon_{0i}$ should be proportional to the square root of the absorption intensity, if $\cos\theta$ does not vary much. For **156** and **157** it has been shown that the intensity of the 300 nm absorption is enhanced through mixing of the magnetic allowed (n, π^*) transition with an electric allowed charge-transfer transition (μ_{CT}) of a π electron from the C=C double bond to the antibonding C=O orbital (π(C=C) $\rightarrow$ π^*(C=O))[108]. Such a result comes up, if the n orbital contains an admixture from the C=C bonding orbital. In both compounds **156** and **157** the corresponding charge-transfer transition moment μ_{CT} makes an angle of ca. 40° with the (n, π^*) magnetic moment which

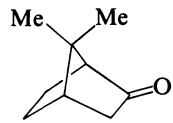
lies in the C=O bond direction[108]. A corresponding situation should occur for **152** and **154**. Hence, for **152**, **154**, **156**, **157** an equation of the type (24) should be obeyed sufficiently well ($\Delta\varepsilon_{n,\pi^*} \approx m_{n,\pi^*} \cdot \mu_{CT} \cdot \cos 40 \approx$ const. $\sqrt{\varepsilon_{n,\pi^*}}$). This is demonstrated by the data in Table 8. These data show also that in the series of cyclic ketones, indeed, similar homoconjugation effects should be operative.

TABLE 8. Absorption and CD characteristics of a series of cyclic ketones

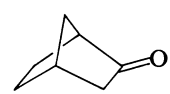
	Absorption		Circular dichroism[105,108]		
Compound	λ(nm)	ε(l mol^{-1} cm^{-1})	λ(nm)	$\Delta\varepsilon$(l mol^{-1} cm^{-1})	$\Delta\varepsilon/\varepsilon$
152	297	27[b]	297	−1.2	−0.0044
153	292	70[b]	292	+6.2	+0.089
156	298	110[a]	298	+12.0	+0.109
157	308	290[a]	308	+19.0	+0.066

[a] From Ref. 108.
[b] From Ref. 105.

In Ref. 105 the (n, π^*) circular dichroism of the tricyclic ketones **152–155** was analyzed with the aim to see whether the systems must be viewed as inherently chiral chromophores or rather inherently symmetric chromophores, respectively. If they fall more nearly into the inherently symmetric classification the octant rule should be applicable. As a basis for the classification the order of magnitude of the rotational strengths R_{n,π^*} was used together with the assumption that inherently chiral chromophores exhibit rotational strengths which are one order of magnitude larger than those of inherently symmetric chromophores. To be largely free from absolute numerical arguments comparisons with the (n, π^*) CEs of model compounds were done. In particular, it was suggested[105] that, if the cyclopropyl ketone under study has a rotational strength which is close to that of α-fenchocampherone (**159**) or bicyclo[2.2.1]heptan-2-one (**160**), it will fall more nearly into



(**159**)



(**160**)

the inherently symmetric type. If, on the other hand, the (n, π^*) CE resembles that of the unsaturated ketones **156** and **157**, respectively, the underlying chromophore should be inherently chiral and the octant rule cannot be applied. The rotational strengths of the ketones **152–160** are presented in Table 9.

For **152–154** octant projections predict that static chiral perturbers will contribute (according to the octant rule) only little to the overall CE[105]. Therefore, it was suggested[105] that the CE of **152–154** should be mainly associated with inherently chiral chromophores. Remarkably, also to the chromophore of **152** whose rotational strength is rather weak an inherently chiral character was attributed[105]. However, this assignment is not consistent with the classification scheme put forward in Ref. 105 which refers to the order of magnitude of R_{n,π^*}. The rotational strength of **152** is between those of **159** and **160**, which are assumed to have inherently symmetric chromophores. On the other hand, strong support that **152**, indeed, has an inherently chiral chromophore comes from the fit of the (n, π^*) CE into equation 24.

TABLE 9. Rotational strengths of β, γ-cyclopropyl and related ketones[105]

Compound	Absolute configuration	$R_{n,\pi^*} \times 10^{40}$ (c. g. s.)	Octant rule, predicted CE
152	1*R*, 5*S*	−3.1	Weakly (+)
153	1*R*, 5*R*	+20.2	Weakly (+)
154	1*R*, 5*R*	+18.9	Weakly (+)
155	2*S*	−9.0	(−)
159	1*S*	−5.9	(−)
160	1*S*	−1.2	Weakly (−)
156	1*R*	+29.0	
157	1*R*	+51.1	

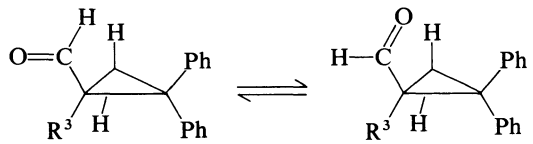
Referring to the very similar rotational strengths of α-fenchocampherone (**159**) and spiro(cyclopropane-1,7′-norbornanone) (**155**) (Figure 13; Table 9) it was suggested[105] that **155** has an inherently symmetric chromophore in which the normal octant perturbers dominate the contributions to the chirality of the (n, π^*) transition.

In view of the preceding finding that the magnitudes of the rotational strengths of **152** and **156** differ by a factor of ten, but both have the same type of chromophore (inherently chiral) the attribution of inherently symmetric character to the chromophore of **155** is questionable. The correct prediction of the sign of the (n, π^*) CE of **155** with the octant rule may be fortuitous (Table 9). The contribution from inherent chirality may be of the same sign as that from the inherently symmetric chromophore. Using **160** as a reference one can see from Table 9 that the effect of the cyclopropane ring (**155**) is more pronounced than that of the gem-dimethyl group (**159**). If the contribution from the inherently symmetric chromophore is $R_{n,\pi^*} \approx -3 \times 10^{-40}$ c.g.s. (intermediate between **159** and **160**), inherent chirality would contribute -6×10^{-40} c.g.s. to the overall rotational strength, i.e. the chromophore of **155** would be more of the inherently chiral type.

d. Open-chain aldehydes and ketones

Due to considerably increased conformational mobility acyclic carbonyl derivatives generally give optical rotations or Cotton effects, respectively, which are substantially lower than those of their cyclic counterparts. This is seen in Table 10 where absorption and circular dichroism characteristics of 2,2-diphenylcyclopropanecarboxaldehydes are given. The data in Table 10 show that the position of the (n, π^*) band absorption maxima varies considerably with the nature of R^3. The increase in $\Delta\varepsilon$ is roughly paralleled by an increase in ε.

As is found for cyclopropanecarboxaldehyde[17] one can assume that the 2,2-diphenyl-cyclopropanecarboxaldehydes exist as an equilibrium of the bisected s-*cis* and s-*trans* forms (**XXXIII**, **XXXIV**). For steric reasons in these compounds the s-*trans* form is



(**XXXIII**) (**XXXIV**)

probably preferred. If, however, R^3 is a rather polar group electrostatic interactions of the R^3–C and C=O dipoles may favor the s-*cis* form (**XXXIV**).

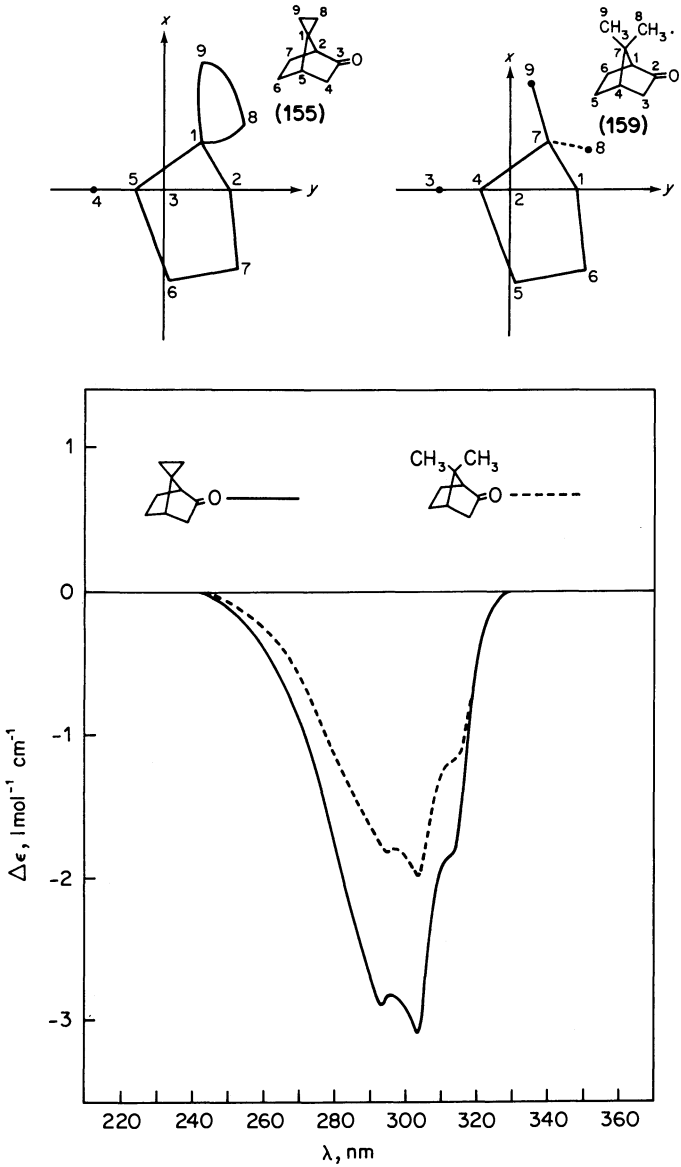


FIGURE 13. CD spectra and octant projections of spiro (cyclopropane-1,7'-norbornanone) (**155**) and α-fenchocampherone (**159**)[105]. *Reprinted with permission from Lightner and Beavers,* J. Am. Chem. Soc., **93**, *2677, Copyright (1971) American Chemical Society*

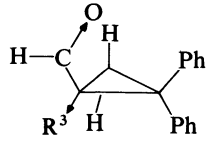
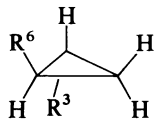


TABLE 10. (n, π^*) Absorption and CD characteristics of 2, 2-diphenylcyclopropanecarboxaldehydes[a]

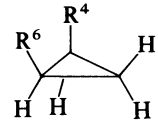
		Absorption[b]		Circular dichroism[b]		
Compound	R^3	λ(nm)	ε(l mol^{-1} cm^{-1})	λ(nm)	$\Delta\varepsilon$(l mol^{-1} cm^{-1})	Ref.
61	H	292	44.2	—	−0.8[c]	11
62	Me	287	54.3	—	−0.9[c]	11
63	MeO	304	130	306	−2.05	39
65	Cl	—	—	294	−3.33	39
66	Br	297	96.5	—	−4.2	11

[a] $R^1 = R^6 = Ph$, $R^2 = R^5 = H$, $R^4 = CHO$.
[b] In dioxane.
[c] Estimated from the amplitudes of the ORD curves.

In Table 11 UV absorption and CD data of a series of aliphatic trans-substituted α-cyclopropyl ketones **II** are summarized. Though the absorption intensity (ε) varies by a



(II)



(IV)

factor of four the (n, π^*) CE ($\Delta\varepsilon$) of the *trans* compounds is almost unaffected by the length of the methylene chain attached to the cyclopropyl or carbonyl moiety, respectively. The magnitudes of $\Delta\varepsilon$ for the 282 nm (n, π^*) bands are smaller than those of the aldehydes (Table 10) by factors between 2 and 7. The variation of the (n, π^*) CE is more pronounced, if the substituents are in the *cis* position (**IV**) (Table 12). The larger variation of the (n, π^*) CE of the *cis*-cyclopropyl ketones surely is due to steric interactions of the *cis*-vicinal groups, which will affect the conformer equilibria. For both the *cis*- and *trans*-α-cyclopropyl ketones the (n, π^*) CE show no direct relationship to the molar rotation $[\Phi]_D$. Hence, the (n, π^*) CE seems to have no significant effect on the rotation at the sodium-D-line.

It has been found that cyclopropyl ketone exhibits a conformer mixture[17]. The preferred component has been identified as the bisected s-*cis* conformer[17]. At the present time, however, it is not clear whether the second conformer (less stable) corresponds to the bisected s-*trans* form or anti-gauche form[17]. On the other hand, on the basis of a theoretical analysis (on the semiempirical INDO-level) and a proton NMR investigation for the *cis–trans* isomeric 2-methylcyclopropyl-1(methyl) ketones **15** and **16** it was suggested[110] that the *trans* compound **15** exists as an equilibrium of the bisected s-*cis* and s-*trans* conformers. The s-*cis* and s-*trans* conformers are separated by a rotational barrier of 5.7 kcal mol^{-1} [110].

TABLE 11. (n, π^*) and (π, π^*) absorption and CD characteristics of aliphatic *trans*-substituted α-cyclopropyl ketones (**II**)[109,110]

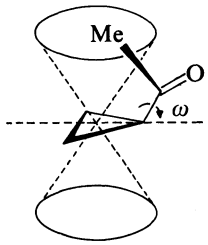
Compound	R^6	R^3	$[\Phi]_D$[a] (deg)	Absorption[b]		Circular dichroism[b]	
				λ(nm)	ε(1 mol^{-1} cm^{-1})	λ(nm)	Δε(l mol^{-1} cm^{-1})
15	COMe	Me	−120	276	23	282	−0.55
				188	6900	—	—
161	$CO(CH_2)_3Me$	Me	−150	279	25	282	−0.60
				189	5900	—	—
162	$CO(CH_2)_7Me$	Et	−140	276	49	282	−0.53
				194	3600	195	−3
163	COMe	$(CH_2)_8Me$	−165	282	80	281	−0.54
				189	4800	195	−3
164	$CO(CH_2)_{12}Me$	$(CH_2)_5Me$	−175	278	54	283	−0.60
				192	6700	195	−3

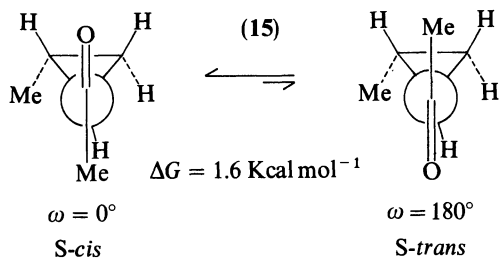
[a] In ether.
[b] In isooctane.

TABLE 12. (n, π^*) and (π, π^*) absorption and CD characteristics of aliphatic *cis*-substituted α-cyclopropyl ketones (IV)[109,110]

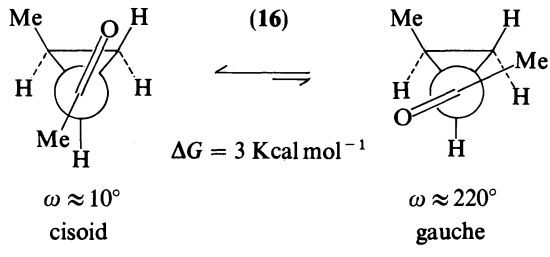
Compound	R^1	R^3	$[\Phi]_D$[a] (deg)	Absorption[b]		Circular dichroism[b]	
				λ(nm)	ε(l mol^{-1} cm^{-1})	λ(nm)	Δε(l mol^{-1} cm^{-1})
16	COMe	Me	+35	283	27	289	+0.44
				192	6200	—	—
165	$CO(CH_2)_3Me$	Me	+50	282	30	288	+0.72
				188	4900	—	—
166	$CO(CH_2)_7Me$	Et	+50	279	50	287	+0.30
				192	4200	195	+1
167	COMe	$(CH_2)_8Me$	+50	283	69	289	+0.15
				188	3000	200	+0.6
168	$CO(CH_2)_4Me$	$(CH_2)_{13}Me$	+70	276	58	287	+0.34
169	$CO(CH_2)_{12}Me$	$(CH_2)_5Me$	+70	276	58	287	+0.34
				192	5500	200	+1

[a] In ether.
[b] In isooctane.





For the *cis* compound **16** the two rapidly equilibrating conformers correspond to a preferred cisoid form ($\omega \approx 10°$) and a less stable gauche form ($\omega \approx 220°$)[110]. For such



binary mixtures (a $\rightleftharpoons$ b) the experimental rotatory strength (at temperature T) R^T is given by equation 25[110].

$$R^T = (R_a - R_b) \cdot \frac{1}{1 - \exp(-\Delta G°/RT)} + R_b \qquad (25)$$

From the study of the temperature dependence of the (n, π^*) CE (and that of the NMR spectra which provide values for $\Delta G°$) it was deduced that the magnitudes of the rotatory strengths of the corresponding conformers of **15** and **16** are almost equal ($R \times 10^{40}$ e.s.u.: −2.4 for s-*cis* (**15**; **II**) and −0.6 for s-*trans* (**15**; **II**); −2.3 for cisoid (**16**; **IV**) and −0.6 for gauche (**16**; **IV**))[110]. For both the compounds the signs of the rotatory strengths of the preferred and less abundant conformers are identical.

The conformer situation should not be affected essentially, if the methyl groups of **15** are substituted by long alkyl chains (**15** → **161–164**). On the other hand, in the series of *cis* compounds **165–169** increasing the alkyl chain length is expected to affect the conformer populations significantly. However, it was suggested[110] that through a particular orientation of the alkyl chain the conformer situation of **16** may be largely retained in the other compounds **165–169**. Only the angle ω of the gauche conformer may vary by $\pm 10°$ in the series **165–169**.

In the two (s-*cis* and s-*trans*) conformations of the trans cyclopropyl ketones the C=O group lies in the symmetry plane of the cyclopropane skeleton. This (local) mirror plane symmetry is slightly perturbed by an alkyl group at the neighbouring ring carbon atom. Hence, as a working hypothesis it was assumed[110] that the chromophore responsible for the (n, π^*) CE can be viewed as inherently symmetric and the (normal) octant rule should be applicable. In terms of octant projections the ring and the 2-methyl group appear in the rear octants for both the s-*cis* and s-*trans* conformers of **15** (Figure 14).

Application of the normal octant rule ((a) in Figure 14) predicts a negative (n, π^*) CE for the abundant s-*cis* conformer of **15**, but a positive one for the less abundant s-*trans* form.

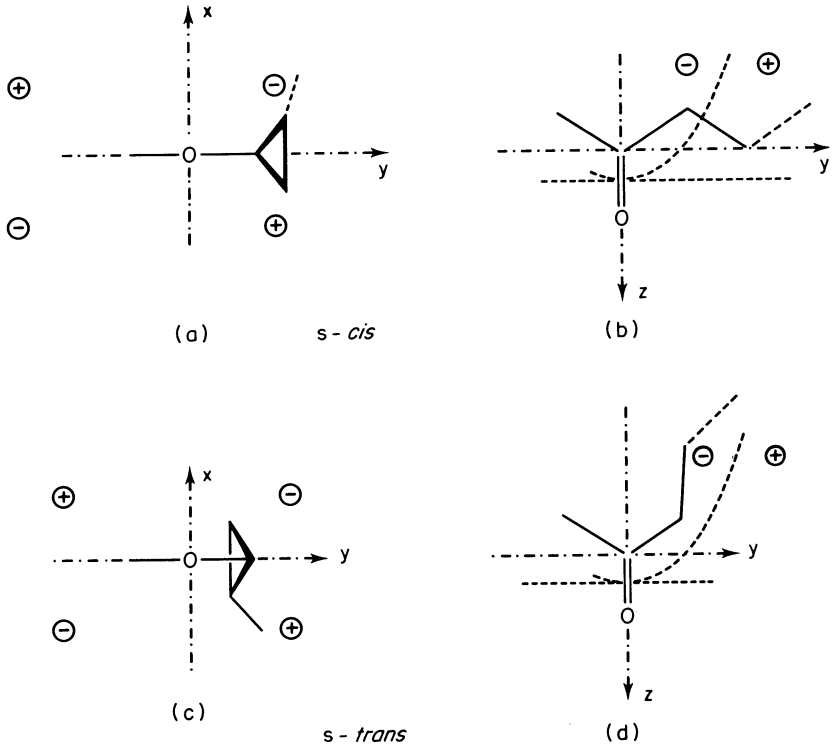


FIGURE 14. Octant views of *trans*-2-methylcyclopropyl-1(methyl) ketone (**15**)

Furthermore, both the s-*cis* and s-*trans* forms should have Cotton effects of almost equal magnitudes, in contrast to the observed negative rotational strengths for both the conformers and the considerably smaller rotational strength of the s-*trans* conformer. In order to retain the theoretical framework of the octant rule it was suggested[110] that a curved surface instead of a plane separates the front and back octants ((b) in Figure 14). Then, for the s-*trans* form of **15** an almost zero (or slightly negative) (n, π^*) CE is predicted which explains the experimental finding qualitatively. Hence, with regard to the discussion in Subsection III.B.4.a the treatment of the (n, π^*) CE of open-chain *trans*-substituted cyclopropyl ketones in Ref. 110 falls into the category of an *a posteriori* explanation of observations.

The situation is different for the series of *cis* compounds **16**, **165–169** (Figure 15). For the (+)-*cis* compound **16** (COMe → R^1, Me → R^3) the methyl group comes into a front octant yielding a positive contribution to the (n, π^*) CE and it is immaterial whether one refers to a nodal plane or a curved surface separating the octants (Figure 15). For the gauche conformer the ring and the methyl group appear in a rear octant. In terms of the modified octant rule with a curved surface separating back and front octants for the cisoid conformation of **16** a positive CE of medium intensity would be predicted. This results from the methyl group penetrating into a (positive) front octant and the partial compensation by the contribution of the ring in a (negative) rear octant. The less abundant gauche conformation of **16** should have an almost zero (n, π^*) CE or a very small (positive

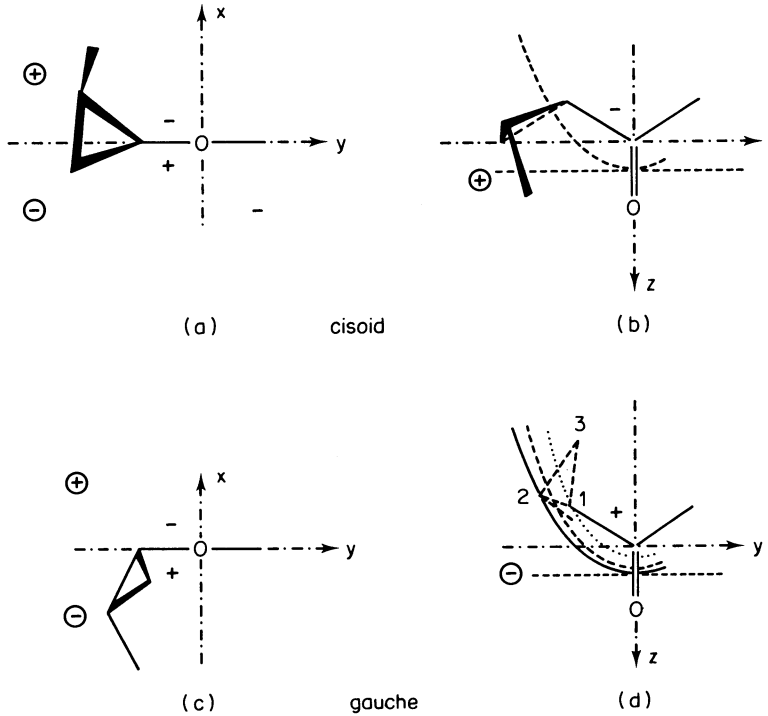


FIGURE 15. Octant views of *cis*-2-methylcyclopropyl-1(methyl) ketone (**16**)[110]

or negative) CE, respectively, depending upon the location of the curved surface. In Ref. 110 it is assumed that in the cisoid conformations the magnitude of the (n, π^*) CE does not vary much, the CE of the gauche form, however, will become more negative, if the torsional angle ω is changed ((b) in Figure 15). In this way, the variation of the (n, π^*) CE of the *cis* compounds (Table 12) was related to the change of ω with the length of the alkyl chain[110]. It is an open question, however, whether the above simple model suffices to explain the (n, π^*) optical activity of the *cis*-substituted cyclopropyl ketones. In these compounds the cyclopropane and carbonyl moieties are skewed relative to one another. Therefore, there will be contributions from the inherent chirality of the system and it is not clear whether these contributions can be neglected. For the (π, π^*) CEs of the compounds in Tables 11 and 12 Kuriyama and coworkers' proposal[101] seems to be obeyed for the *trans* compounds **162–164**. Accordingly, for cyclopropyl ketones with ideal s-*cis* and s-*trans* bisected conformations the sign of the (π, π^*) CE should be determined by the 2-substituent. As the s-*cis* forms are preferred for **162–164** the compounds should have a negative (π, π^*) CE ((a) in Figure 14), as is observed.

Application of Kuriyama's rule to the *cis* compounds does not allow secure inferences to be made. According to Figure 15(b) the cisoid forms should contribute a slightly positive CE. On the other hand, the gauche forms should have a negative (π, π^*) CE. Though the gauche forms are less abundant it may be that they have a strong negative (π, π^*) CE from inherent chirality. In this way, the weak positive CE of the abundant cisoid form may be outweighed by the strong CE of the less abundant gauche form.

IV. VIBRATIONAL CIRCULAR DICHROISM OF CYCLOPROPANES

A. Electronic and Vibrational Circular Dichroism

Vibrational optical activity, in particular, vibrational circular dichroism (VCD), has become a topic of considerable interest since 1970[1, 111–113]. The phenomenon is related to the different absorption of left- and right-circularly polarized infrared radiation and, hence, involves excitations of molecules into particular vibrational states.

As is common in infrared spectroscopy of organic compounds, in the study of VCD reference is also made to characteristic (functional) group frequencies which result from nuclear motions largely localized at a particular bond or set of bonds to a common center (the 'vibrational chromophores'). Several advantages of VCD over electronic CD for structural research can be anticipated. First, using VCD, stereochemical information can be inferred from more subunits of a chiral compound; for instance, from vibrations of C–H units and other functional groups (such as OH, NH_2, C≡N, C=O, COOR etc.). The various vibrational transitions ('characteristic group frequencies') are mostly well resolved. Second, for a given group of atoms the VCD may be investigated for various nuclear motions separately. For instance, one can study C–H stretching and bending (torsional) motions of a Me (or other aliphatic) group.

With regard to the generation of VCD each of the general mechanisms for optical activity apply with appropriate modifications to both electronic and vibrational circular dichroism. In particular, the two-group electric-dipole mechanism ('coupled oscillator mechanism' or, for isoenergetic subgroups, the 'exciton model')[1, 111–113] provides an easy transition from concepts of CD to those of VCD. An essential difference between CD measurements in the ultraviolet region and the infrared spectral region is that CD is associated with electronic excited states of molecules, whereas VCD refers to the electronic ground state. For isoenergetic two-group coupling ('degenerate coupled oscillators', DCO) the rotational strengths of a given couple of vibrational transitions is generally given by equation 26[112, 113].

$$R^{\pm} = 1/2\, Im(\boldsymbol{\mu}_1 \cdot \boldsymbol{m}_1 + \boldsymbol{\mu}_2 \cdot \boldsymbol{m}_2) \pm 1/2\left[Im(\boldsymbol{\mu}_1 \cdot \boldsymbol{m}_2 + \boldsymbol{\mu}_2 \cdot \boldsymbol{m}_1) - \frac{\omega}{2c}\boldsymbol{R}_{12} \cdot (\boldsymbol{\mu}_1 \times \boldsymbol{\mu}_2)\right] \tag{26}$$

In equation 26 $\boldsymbol{R}_{12}$ is the distance vector from group 1 to group 2, $\boldsymbol{\mu}_i$ and $\boldsymbol{m}_i (i = 1, 2)$ are the electric and magnetic dipole transition moments in the groups i for the considered vibrational mode with the angular frequency ω. The last term in equation 26 corresponds to the exciton term in electronic CD. The second term represents the $\boldsymbol{\mu} - \boldsymbol{m}$ mechanism for the generation of optical activity and the first term is due to the inherent chirality of each group. If the vibrations of the groups 1 and 2 have negligibly small magnetic moments ($\boldsymbol{m}_i \approx 0$), as may be the case for functional groups' stretching frequencies, the vibrational optical activity should essentially result from the electric-dipole coupling term in equation 26: $R^{\pm} = \pm\, \omega/4c\, \mathbf{R}_{12} \cdot (\boldsymbol{\mu}_1 \times \boldsymbol{\mu}_2)$. The resulting VCD then only depends on the relative orientation of the two electric transition dipole moments $\boldsymbol{\mu}_i$ which in turn can be determined from the (infrared) absorption spectrum.

An expression which is structurally similar to the last term of equation 26 appears in the (conceptionally simple) 'fixed partial charge' (FPC) model of vibrational CD[1, 111–113]. In this model to each atom i of the molecule an effective charge q_i is attributed. During the vibration this charge is assumed to move rigidly with the nuclei. In order to obtain the required electric and magnetic transition moments in the FPC model a normal coordinate analysis affords the nuclear displacements from the equilibrium configuration of the molecule in an infrared radiation field at a normal-mode vibration frequency. Then, the displacement of the fixed partial charges generates local electric dipoles which couple to

produce a resultant electric-dipole and magnetic-dipole transition moment. The final expression obtained for a transition of the jth normal mode from the ground-state (0) to the first vibrational level is given by equation 27.

$$R_{01}^{j} = \mu_{01}^{j} \cdot m_{01}^{j} = \frac{h}{4c} \sum_{i<k} q_i \cdot q_k \cdot \boldsymbol{R}_{ik} \cdot (\boldsymbol{S}_k^j \times \boldsymbol{S}_i^j) \tag{27}$$

In equation 27 $\boldsymbol{R}_{ik}$ is the distance vector of the equilibrium internuclear distance between the atoms k and i. $\boldsymbol{S}_k^j$ and $\boldsymbol{S}_i^j$ are the vector components associated with the matrix that transforms normal coordinate displacements to internal coordinate displacements (along and perpendicular to bond directions). The sum is over the atoms and transformation vectors associated with the jth vibrational normal coordinate.

The FPC model ignores any charge redistribution during molecular vibrations. Hence, shortcomings of the model in describing VCD effects quantitatively can be anticipated. More advanced theoretical treatments of VCD are summarized in Refs 112 and 113.

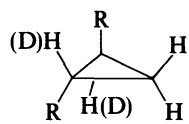
With regard to stereochemical purposes a further model for the interpretation of VCD shall be mentioned. In a series of compounds with a common $CH_2CH_2CH^*$ fragment in the C–H stretching region three VCD bands are found with alternating sign patterns, $(+-+)$ or $(-+-)$, depending upon the stereochemical arrangement of that $CH_2CH_2CH^*$ fragment. This fragment may be viewed as an inherently chiral (vibrational) chromophore.

In the context of present VCD investigations the study of the VCD of cyclopropanes serves, on the one hand, to have models to verify or disprove the applicability of a given VCD theory. On the other hand, empirical correlations are sought for which relate VCD features to well defined structural features.

B. Vibrational Circular Dichroism of Trans-1,2-Disubstituted Cyclopropanes

1. C–H vibrations

In Ref. 2 the VCD of a number of *trans*-1,2-disubstituted cyclopropanecarboxylic acid derivatives (**10–12**, **170**, **171**) in the region 3200–1250 cm^{-1} are reported. Exchanging



R	COOH	COOMe	CN	COCl	$CONH_2$
	10	**11**	**12**	**170**	**171**

hydrogen by deuterium enabled also studies of isotopically substituted compounds. This will provide information about vibrations of particular C–H subunits. For the above compounds, for instance, the methylene group (CH_2) vibrations or the *trans*-vicinal C–H (HCCH) group vibrations may be studied in isolation.

In Figure 16 the VCD and (infrared) absorption spectra in the CH stretching region of (+)-dimethyl *trans*-cyclopropanedicarboxylate with d_3-methyl groups (**11**-d_6) and *trans*-vicinal deuterium atoms (**11**-d_8) are displayed. In these spectra the VCD signals at 2960 cm^{-1} due to carbomethoxy Me stretching vibrations are absent. Effects result only from ring CH modes. Comparing these spectra reveals that the strong negative feature at about 3060 cm^{-1} and the distinct positive shoulder at 3080 cm^{-1} disappear upon deuteration (**11**-d_6 → **11**-d_8). Similarly, in absorption the 3070 cm^{-1} band of **11**-d_6 disappears upon deuteration (**11**-d_8). Hence, the highest and lowest energy CH absorption bands ($\tilde{\nu} \approx 3100$ cm^{-1}, $\tilde{\nu} \approx 3020$ cm^{-1}) result from (antisymmetric (as) and symmetric (s)) combinations of C–H vibrations of the apex CH_2 moiety [2, 17]. The oppositely signed VCD

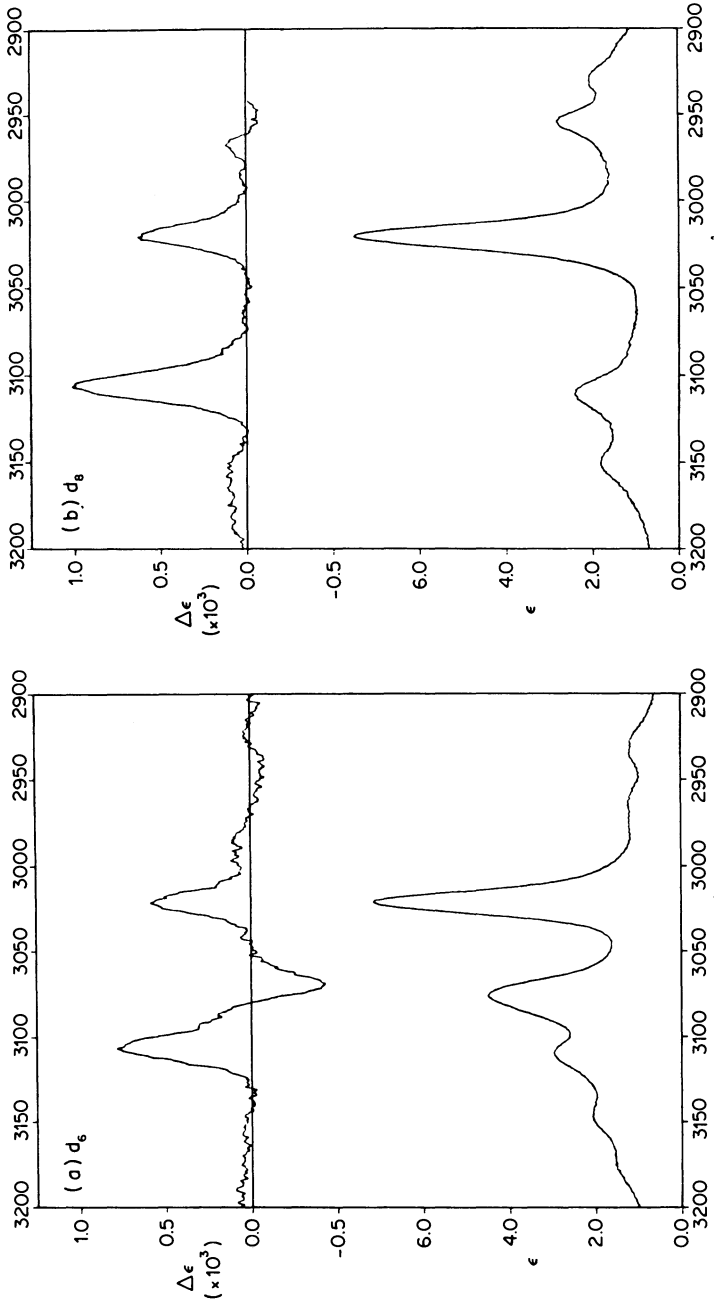
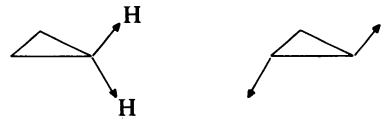


FIGURE 16. VCD and absorption spectra in the CH stretching region of (+)-dimethyl *trans*-1, 2-cyclopropanedicarboxylate with d_3 methyl groups: (a) d_6-ester (**11**-d_6), (b) d_8-ester (**11**-d_8) in CCl_4[2]. *Reprinted with permission from Heintz and Keiderling,* J. Am. Chem. Soc., **103**, 2395, *Copyright (1981) American Chemical Society*

couplet at 3080 cm^{-1} and 3060 cm^{-1} can be associated with the antisymmetrically and symmetrically combined C–H vibrations of the *trans*-vicinal arranged C–H groups. For

$\tilde{\nu}_{as}(CH_2)$ $\tilde{\nu}_{as}(HCCH)$



$\tilde{\nu}_{s}(CH_2)$ $\tilde{\nu}_{s}(HCCH)$

the (1*S*, 2*S*)-(+) compounds **10**, **11**, **170**, **171** (or deuterated derivatives thereof) the antisymmetric and symmetric ring CH_2 stretchings (at 3100 cm^{-1} and 3020 cm^{-1}) are associated with positive VCD bands. On the other hand, the *trans* CH stretches exhibit oppositely signed VCD bands. FPC calculations using pseudoatoms for the substituents have reproduced the above + + − + VCD sign pattern (from high to low energy)[2]. In the series of compounds **10**, **11**, **170**, **171** the VCD associated with the above stretches is qualitatively not changed by deuteration (but merely shifted in frequency). This implies that the apex CH_2 and *trans*-vicinal CH stretches are rather independent of each other[2].

The situation changes markedly, if the VCD of the dinitrile **12** is considered (Figure 17). At highest energy (3120 cm^{-1}) **12** has a negative VCD band. Furthermore, the largest VCD feature is found at 3055 cm^{-1} (and remains positive). This strong central band disappears in the absorption and VCD spectra of **12**-d_2. Hence, the intense 3055 cm^{-1} positive VCD feature corresponds to *trans*-vicinal CH stretches. In **12**-d_2 the remaining VCD is extremely weak. This can be taken as an indication that in **12** significant apex–*trans* CH interactions occur[2]. Obviously, for **12** the VCD signals are entirely due to *trans* CH stretches or apex–*trans* interactions. The VCD behavior of **12** which is different from that of the other acid derivatives can be attributed to distinct conjugation effects of the nitrile groups with the cyclopropane ring.

Apart from stretching vibrations the VCD of C–H bending and CH_2 scissoring modes (1500–1250 cm^{-1}) are also amenable to experimental investigations. In general, both the absorption and VCD signals of deformation modes are larger than those corresponding to stretchings. In Figure 18 the VCD spectra of **11**-d_6 and **11**-d_8 in the CH_2 bending region are displayed. The positive VCD feature near 1375 cm^{-1} appears to be the CH_2 scissor mode of **11**. This positive VCD band is considerably shifted to 1430 cm^{-1} in the acid chloride **170**[2].

The negative VCD feature of **11**-d_6 at 1430 cm^{-1} has contributions from the *trans* CH moiety. Similarly, the positive VCD at 1340 cm^{-1} must also involve *trans*-vicinal CH deformations. Referring to the assignments of infrared frequencies of monosubstituted cyclopropanes[17] the 1340 cm^{-1} VCD band should be associated with CH bendings in-plane. In contrast to the situation for the stretching modes the CH_2 and HCCH deformation modes seem to interact more strongly[2].

2. *Functional group vibrations*

In Figure 19 the VCD and infrared absorption spectra of the dimethyl ester **11** in the C=O region is displayed. The strong 1730 cm^{-1} absorption band gives rise to a bisignate

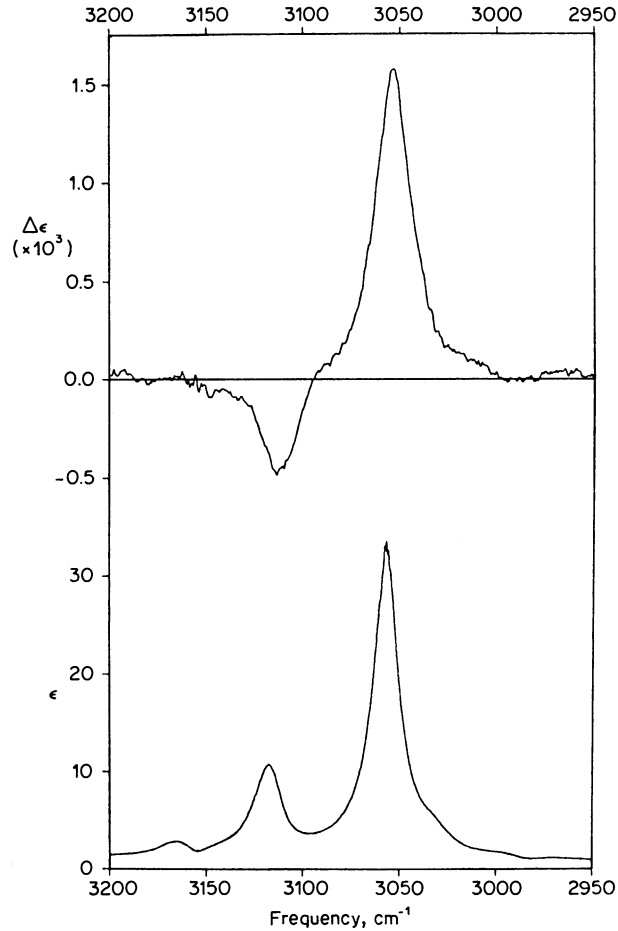


FIGURE 17. VCD and absorption spectra of (+)-*trans*-1, 2-cyclopropanedicarbonitrile (**12**) in the CH stretching region in $CDCl_3$[2]. *Reprinted with permission from Heintz and Keiderling*, J. Am. Chem. Soc., **103**, *2395, Copyright (1981) American Chemical Society*

VCD signal, as is expected from a degenerate coupled oscillator (DCO) model for the two interacting C=O stretching modes with strong electric transition moments. A careful analysis of the VCD spectrum of **11** has revealed two shoulders in the C=O stretching region, i.e. there exists at least three bands in that region. In line with the previous discussions it is evident that the spectrum should reflect (s-*cis*, s-*trans*) conformer equilibria. A DCO analysis predicts the *trans–trans* and *cis–cis* conformers of **11** to have a VCD couplet with a negative band to lower energy. The same result was found on the basis of FPC calculations[2]. Both these models predict a sign pattern for the mixed *cis–trans* conformer of **11** which is opposite to that of the *trans–trans* and *cis–cis* conformers. The DCO model predicts VCD signals for the *trans–trans* conformer which are tenfold larger

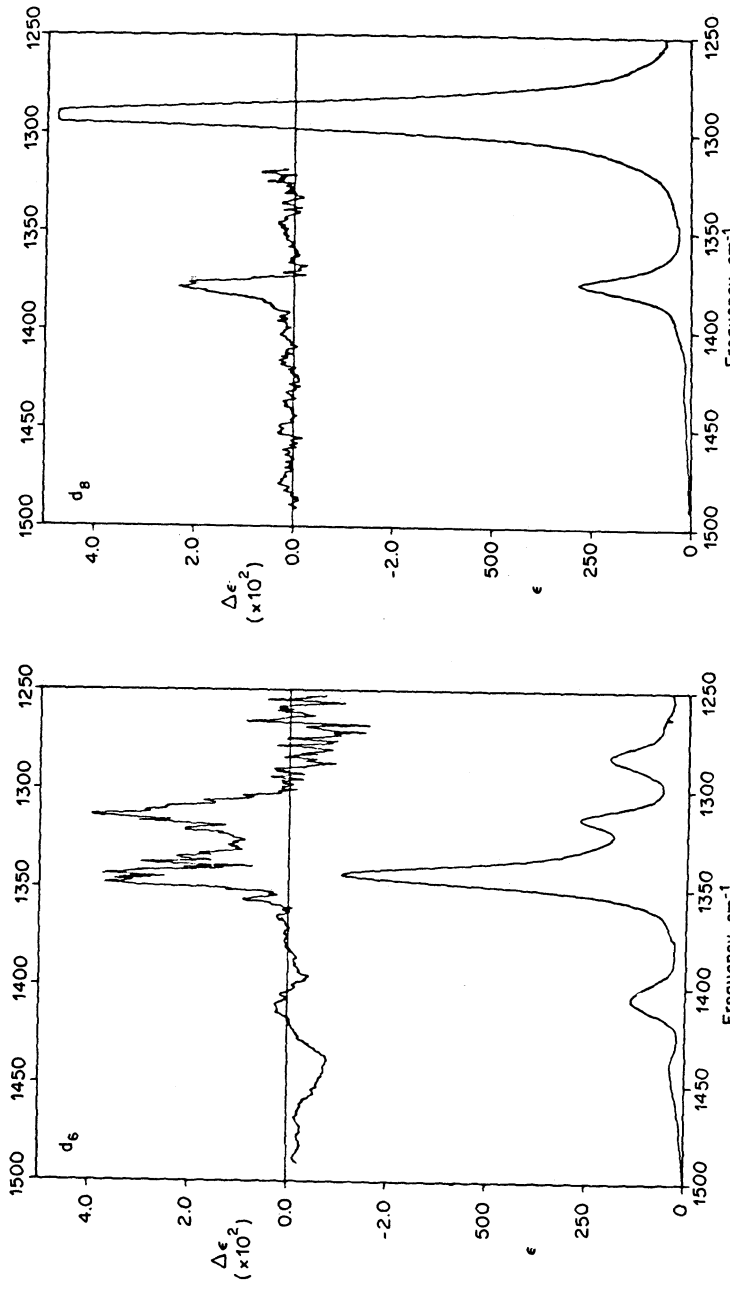


FIGURE 18. VCD and absorption spectra of deuterated (+)-dimethyl *trans*-1,2-cyclopropanedicarboxylates **11**-d_6 and **11**-d_8 in the CH_2 bending region in CCl_4.[2] *Reprinted with permission from Heintz and Keiderling,* J. Am. Chem. Soc., **103**, *2395, Copyright (1981) American Chemical Society*

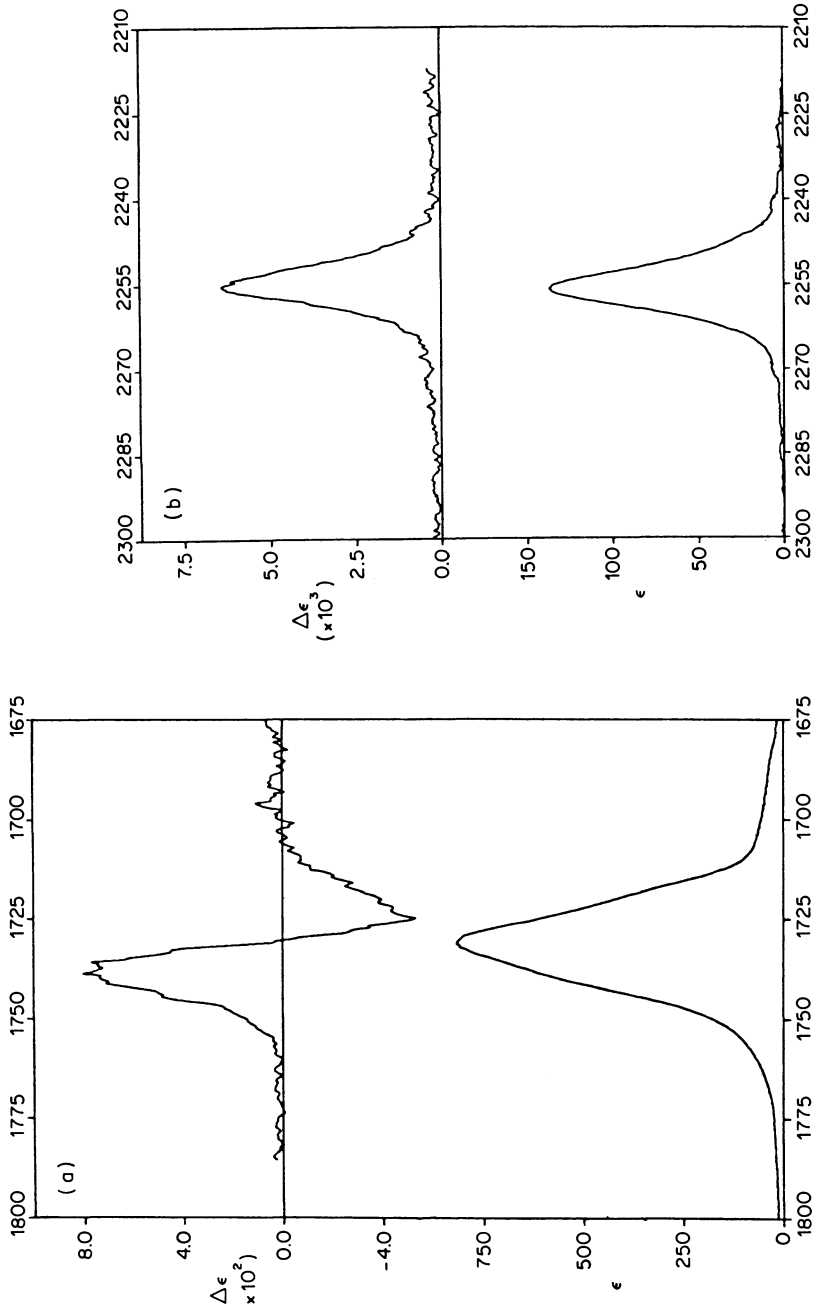


FIGURE 19. VCD and absorption spectra of the C=O stretching region of (+)-dimethyl *trans*-1,2-cyclopropanedicarboxylate (**11**) (a) and the C≡N stretching region of (+)-*trans*-1,2-cyclopropanedicarbonitrile (**12**) (b)[2]. *Reprinted with permission from Heintz and Keiderling,* J. Am. Chem. Soc., **103**, *2395, Copyright (1981) American Chemical Society*

than the VCD signals of the *cis–cis* conformer[2]. In contrast to the dimethyl ester **11** the dinitrile **12** exhibits a monosignate VCD spectrum in the C≡N stretching region around 2255 cm^{-1} (Figure 19). DCO model calculations for **12** attribute to the C≡N stretch a VCD signal which is ca. 20 times smaller than the observed band. The *g*-value ($\Delta\varepsilon/\varepsilon$) for the dinitrile **12** stretch ($g \approx 4.5 \times 10^{-5}$) is half of that of the dimethyl ester **11** ($g \approx 9 \times 10^{-5}$). This means that **12** does not only behave differently from the acid derivatives with regard to the VCD of the C–H stretching vibrations (reflecting properties of the cyclopropane moiety), but also to the stretching vibrations of the substituents (COR vs. C≡N).

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CHAPTER **3**

Nuclear magnetic resonance and infrared spectra of cyclopropanes and cyclopropenes

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I. INTRODUCTION

The aim of this review is to show something of the NMR and IR characteristics of cyclopropane and cyclopropene rings both alone, in the presence of substituents and when built into more complex ring systems. Whereas for cyclopropanes a division into five subheadings has been made, the smaller amount of subject matter in the later sections has not impelled such a subdivision.

Chemical shifts quoted as δ or ppm are downfield from tetramethylsilane (TMS) in the case of ^1H and ^{13}C nuclei. Unless otherwise stated, fluorine chemical shifts are quoted with respect to $CFCl_3$. The standard for other chemical shifts is indicated at the point of citation.

The literature coverage is up to July 1985.

II. ^{1}H CHEMICAL SHIFTS OF CYCLOPROPANES

The principal characteristic of the ^1H-NMR spectrum of cyclopropane is the unusually high field, 0.2 ppm (downfield from TMS), at which the protons absorb[1] with respect to 'normal' methylene protons. Indeed this high field shift is of considerable diagnostic value.

The origin of this effect has been the subject of many investigations. The molar susceptibility of cyclopropane was found[2] to be -39.9×10^{-6}, as compared with a calculated value[3] from Pascal's numbers of -32×10^{-6} and the difference between these two values has been attributed to a ring current. This ring current is thought by many to bring about the enhanced shielding.

Cyclopropane belies its simple appearance[4]. Hybridization of the carbon–hydrogen bonding orbitals in cyclopropane is close to sp^2 (actually $sp^{2.28}$)[5] and that of the orbitals forming the carbon–carbon bonds is $sp^{4.12}$ [5]. It was proposed that these latter orbitals lie outside the line connecting adjacent carbon atoms such that the angle between the axes of the $sp^{4.12}$ hybridized orbitals is 104°. The CCC internuclear angles are clearly 60° and so the carbon–carbon bonds are bent by 22°.

The hybridization of the carbon–hydrogen bond orbitals in cyclopropane is clearly similar to those in alkenes. However, the chemical shifts of these two types of proton are appreciably different and factors other than hybridization must be responsible.

^{13}C chemical shifts of cyclopropane, and its derivatives, are again at a higher field than is usual for methylene carbons; for cyclopropane $\delta C = 2.80$ ppm[6,7].

Lazzeretti's group[8], collating recent studies, has stated that as a 'mere consequence of symmetry' planar molecules possess a paramagnetic axial vortex brought about by σ electrons flowing around the highest symmetry axis. Calculations indicate that in cyclopropane, there is an anomalous high field value of the perpendicular component, σ_{33}, of the carbon magnetic shielding tensor. These calculations have reinforced earlier experimental work of Grant and coworkers on both cyclopropene[9] and cyclopropane[10] By means of cross-polarization spectroscopy at 20 K the ^{13}C shift tensors for a wide variety of olefins were determined and are given in Table 1. Whereas two of the components are at fairly typical aliphatic values, σ_{33}, which is perpendicular to the plane of the molecule, is at abnormally high field in accord with the circulation of electrons in the

TABLE 1. ^{13}C shift tensors for CH_2 in cyclopropane and cyclopropene

	σ_{iso} (liq)	σ_{11}	σ_{22}	σ_{33}
Cyclopropane	2.3	40	29	−59
Cyclopropene	−3.8	22	2	−30

plane of the cyclopropane. The characteristic magnetic properties of the simplest aromatic system, the cyclopropenyl cation, have been the subject of an analogous calculation[11].

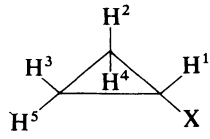
Burke and Lauterbur[6] noted the enhanced shieldings both of ^1H and ^{13}C of cyclopropane with respect to other cycloalkanes, and they considered the existence of a ring current to rationalize these, and also the enhanced molecular susceptibility.

The effect of substituents on the ^1H-NMR spectra of cyclopropanes has been examined by the groups of Roberts[1], Scherr[12] (this work includes a number of organometallic derivatives) and Wiberg[13]. The α-carbon was, as usual, deshielded by an electron-withdrawing group such that for nitrocyclopropane δH_α was 4.2144 in carbon tetrachloride; the corresponding absorptions for less strongly electron-withdrawing substituents were at higher field although no precise correlation between chemical shift and any electron-withdrawing parameter of the substituent was found[13]. Good correlations were noted for the α-proton chemical shifts of monosubstituted cyclopropanes and those of the corresponding methyl, *n*-propyl and isopropyl compounds. Two noteworthy effects were observed:

(1) a plot of the α-proton chemical shifts of monosubstituted cyclopropanes vs. those of the isopropyl derivatives (which, sterically are closest to the cyclopropanes at C_α) gave a slope of 1.34;

(2) anisotropy of the carbon–halogen bonds leads to pronounced deviations for these compounds.

The ^1H chemical shifts of the β-protons of **1** were also reported with great accuracy[13]. The dependence on substituent character is now more complex and when the substituent is



(1)

saturated is related to the quantity $\Delta\chi$ in the McConnell equation (equation 1)[14] which is concerned with the chemical shift difference brought about by the difference in anisotropy between the C–X and C–H bonds. No change in geometry is assumed; *R* is separation of the proton in question

$$\Delta\delta = \delta_{C\text{-}H} - \delta_{C\text{-}X} = \frac{\Delta\chi}{3R^2}(1 - 3\cos^2\theta) \tag{1}$$

from the electrical centre of gravity of the C–X bond and θ is the angle between the axis of the C–X bond and the line defining *R*, and $\Delta\chi$ is given by equation 2.

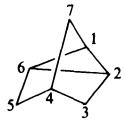
$$\Delta\chi = (\chi_{11} - \chi_\perp)_{C\text{-}X} - (\chi_{11} - \chi_\perp)_{C\text{-}H} \tag{2}$$

where, in turn, χ_{11} represents the magnetic susceptibility along the *z* (or bond) axis and $\chi_\perp$ represents the magnetic susceptibility along the *x* or *y* axis of the bond in question. For those cases in which $\Delta\chi$ is positive the protons *trans* to X absorb at lower field than do the *cis* protons and vice versa. Examples are provided by **1**, X = I, for which $\delta H^2 = 1.04$ and $\delta H^4 = 0.75$ (anisotropy increases down the periodic table) and corresponding values for **1**, X = OH of 0.40 and 0.48 (anisotropy increases across the periodic table from fluorine to carbon).

More complicated behaviour is shown[13] when the substituent contains a double bond, possibly because there exists a preferred conformation with respect to the cyclopropane

ring. Empirically it was found that of the protons β to the substituent, those that are *cis* are generally deshielded with respect to the *trans* counterparts; an exception is however noted in the case of phenylcyclopropane. Wiberg[13] has collated ^{1}H-NMR data for twenty-two monosubstituted cyclopropanes.

The anisotropy of the cyclopropane ring was calculated by Forsén and Norin[15], using the point dipole approximation. In one of several examples they noted that H_4 of nortricyclene, **2**, absorbed 0.3 ppm to higher field than the corresponding proton of

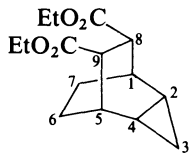


(2)

(3)

norbornane, **3**. This shift together with a correction added for the anisotropy of the C(1)–C(2) and C(1)–C(6) bonds, ca. 0.11 ppm from the point dipole method and a value $\Delta\chi = 5.5 \times 10^{-30}$ cm^3 mol^{-1} for C–C single bond, is construed as the anisotropic effect of the cyclopropane ring on H_4 in **2**. This leads via the point dipole approximation to $\Delta\chi$ (cyclopropane) $= 20 \times 10^{-6}$ cm^3 mol^{-1}. Other more or less similar values were reported[15].

In order to study the long-range shielding effect of a cyclopropane ring, Tori and Kitahonoki[16] employed a series of more or less rigid molecules such as **4** and **5**, one of which contains a cyclopropane ring. In **4** H_1 and H_5 are shielded by 0.30 ppm and H_8 and



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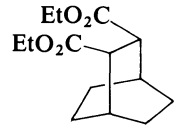
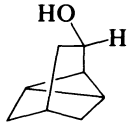


(5)

H_9 by 0.11 ppm with respect to values in **5**. These cyclopropane ring-induced shifts were accounted for in a reasonable manner using bond anisotropy values; indeed the data were less well rationalized when a ring current in the cyclopropane ring was invoked.

Poulter and coworkers[3] have developed a model for reasonably accurate estimation of the anisotropy of a cyclopropane ring. This model involves electrons precessing in a circle which circumscribes the three-membered framework, though the authors note that at the time of writing proof of the existence of a ring current in the cyclopropane ring is still awaited. Their resultant shielding map is shown in Figure 1: positive contours represent shielding induced by the cyclopropane ring and negative contours correspond to deshielding. Good agreement with the experimental shifts was shown for **4** and **6**, although



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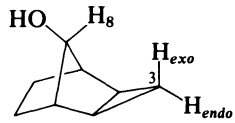

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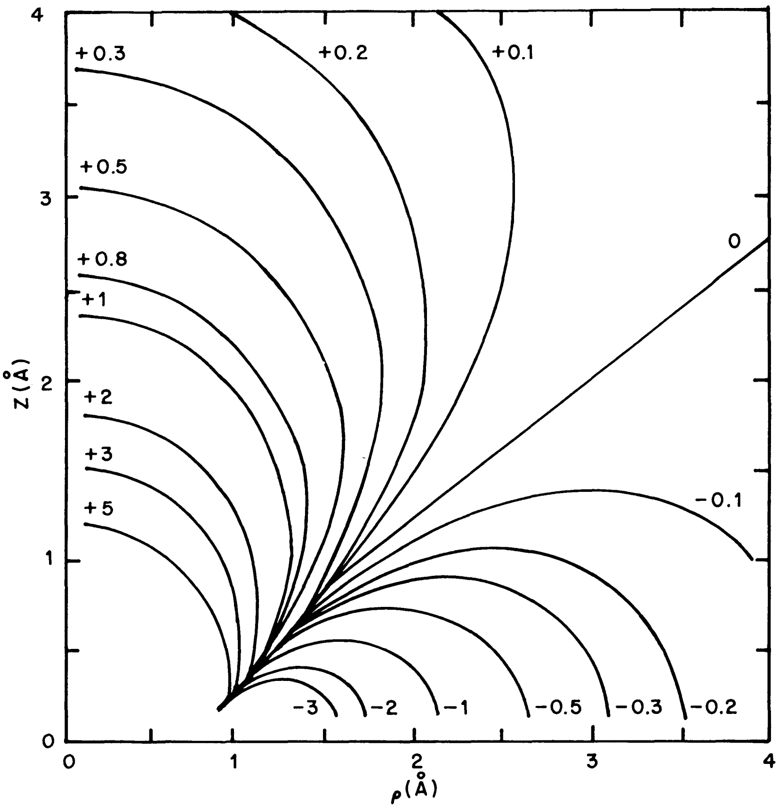
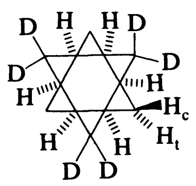


FIGURE 1

significant deviation exhibited by **7**[17] in which there is large non-bonded interaction between H_8 and H_{3exo}. This interaction has the effect of moving H_8 downfield to a value of 3.5 ppm. Such interaction probably finds its best expression in the (non-cyclopropanoid) bird-cage compounds. Also steric interactions are probably the cause of deviations in **8**[3,18];



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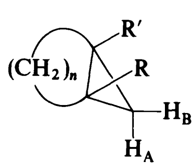
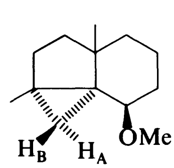


(9)



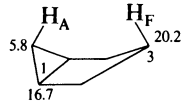
(10)

here $\delta H_c = 0.66$ (1.28) and δH_t -2.16 (-0.28) where the figures in parentheses are the contributions of the cyclopropane ring to the chemical shift.

Dauben and Wipke examined both the chemical shifts and coupling constants of a variety of compounds of the general type **9** and exemplified by bicyclo[3.1.0]hexane and functionalized derivatives such as **10**[19]. The geminal proton with the *endo* configuration

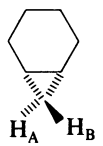
resonates at lower field than its *exo* counterpart; in the case of **10** the respective chemical shifts of H_A and H_B are 0.53 and −0.46 ppm respectively. From many data it was found that the *endo* proton (H_A) of the methylene group of a cyclopropane was deshielded with respect to the *exo* proton (H_B) in the cases of a bicyclo[3.1.0]hexane with one ring junction substituent or of a bicyclo[4.1.0]heptane nucleus carrying one substituent at the ring junction and a hydroxyl group on the six-membered ring.

The deshielding effect in bicyclo[3.1.0]hexanes[19] is considered to have its origin in the relatively close approach of H_A and H_F in **11**[20], considered to be ca. 2 Å with the proviso, later confirmed[21], of a flattened boat conformation for **11**.



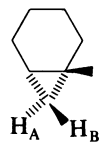
(11)

The same paper[19] deals with the diamagnetic anisotropic shielding of a proton by a carbon–carbon bond. This was demonstrated from a comparison of the chemical shifts of **12** and **13** which are displayed underneath the structures in ppm. In the latter compound



−0.04 0.63

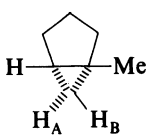
(12)



0.05 0.18

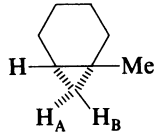
(13)

the *endo* proton still absorbs at higher field though now by a smaller margin. Different ring sizes (and associated differences in diamagnetic shielding) can also affect the value of $\Delta\chi$ as can be seen by inspection of **14**–**17**; the McConnell equation had only limited success in predicting these shifts.



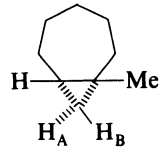
0.30 0.10

(14)



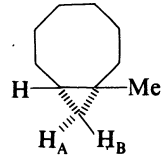
0.19 0.34

(15)



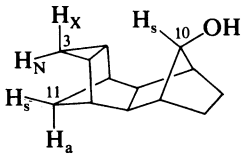
0.16 0.46

(16)

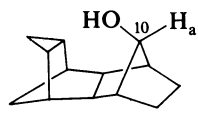


0.10 0.34

(17)

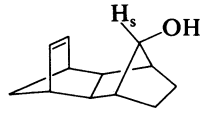


(18)

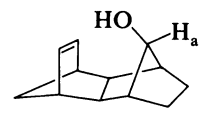


(19)

Rigid fused-ring compounds such as **18** and **19** have been investigated and it was shown[21] that for this pair the protons H_{10s} and H_{10a} absorb at 5.00 and 3.75 ppm respectively. For **20** and **21** the corresponding data are 4.80 and 3.60 ppm and for **22** and **23**, 4.42 and 3.93 ppm. The significant values of $\Delta\delta$ in these pairs of epimers were attributed



(20)



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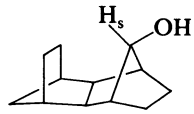

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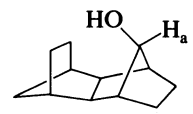


(23)

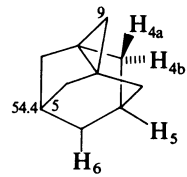
to magnetic anisotropy of neighbouring C–C and C–H bonds and also to intramolecular van der Waals' interactions; polarization factors are probably unimportant in these molecules. The ring current model for cyclopropane implies that substituents in or near to the plane of the three-membered ring are deshielded (and those above the ring are shielded). It was surprising that H_{10a} in **19** experienced an upfield shift.

Absence of any IR band in the region 3300–3600 cm^{-1} suggests that the requisite conformation for intramolecular cyclopropane HO bonding can not be adopted; the authors postulate that a compressional interaction may so distort the intramolecular electric fields as to bring about the dipolar shielding.

The *syn* protons H_s in **18**, **20** and **22** are considered to be anomalously deshielded and ring anisotropy effects are calculated[22] to account for 0.5 ppm of the 1.08 ppm deshielding. This last figure is arrived at as the difference, $\Delta\delta$, between H_{10s} in **18** and H_7 in 7-substituted norbornane. Steric deshielding is proposed to account for the remaining downfield shift.

In **18** the cyclopropyl protons H_{3X} and H_{3N} absorb at -0.01 and 0.53 ppm respectively; the C(11) protons H_{11s} and H_{11a} absorb at 0.95 and 0.49 ppm respectively. On the basis of a ring current it is expected that protons located above the cyclopropane ring should be shielded and the chemical shift observed for H_s does not bear this out. However there are clearly severe non-bonded interactions between H_{11s} and H_{3N} in **18** and the steric deshielding experienced by those protons accounts for the anomalous order of shifts for H_{11s} and H_{11a}. The local diamagnetic shielding environment for the 'external' protons H_{11a} and H_{3X} is accordingly enhanced so that these protons absorb at high field.

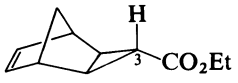
In degassed benzene the protons H_{4a} and H_{4b} of 1,3-dehydroadamantane (**24**) absorb



(24)

respectively at 1.15 and 1.91 ppm[23]. The large chemical shift difference, 0.76 ppm, is consistent with their positions above (H_{4a}) and nearer the side (H_{4b}) of the anisotropic cyclopropane ring. The protons H_5 (δ2.73) and H_6 (δ2.05) are both rather deshielded for their type and this is attributed to their location with respect to the cyclopropane ring[24].

Probably the earliest manifestations of the induced shielding brought about by the purported ring current of the cyclopropane ring were those of Sauers[25] who reported that the vinyl protons of **26** were shifted upfield by 0.6 ppm with respect to **25** on account of



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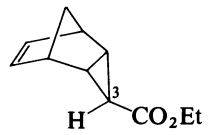


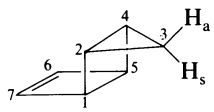
(26)

(27)

shielding induced by the cyclopropane ring[45]. It is noted that the chemical shift of the C(3) proton is appreciably different in the two cases; for **25**, 2.48 ppm and for **26**, 1.34 ppm.

At about the same time Wiberg and Bartley[26] found that the *endo* cyclopropane group of **27** brought about a shielding of the vinyl protons to δ5.64 as compared with δ5.94 in norbornene.

Recently, the two isomers **28** and **29** were made by Grimme and Köser[27]; the former was assigned the *anti* structure shown by the shielding of the allylic protons H_1 and H_5 as well as by the small coupling, $J < 1$ Hz, with the tertiary cyclopropyl protons H_2 and H_4; for **28** δH_1, $H_5 = 2.87$ (narrow multiplet) in CCl_4. By way of contrast, in the *syn* isomer (**29**), the allylic protons are deshielded by 0.2 ppm and couple strongly with H_2 and H_4; also δH_1, $H_5 = 3.07$ (*d*, $J = 5$ Hz).



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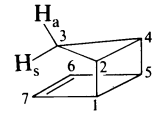


(29)

In **28** the cyclopropyl methylene protons absorb at $H_{3a} = 1.13$, $H_{3s} = 0.88$ ppm respectively; in the stereoisomer **29**, the corresponding chemical shifts are for H_{3a}, 0.28 and for H_{3s}, 1.08 ppm. The unexpected deshielding of H_{3s} in **29** may have its origins in steric compression that overcompensates the shielding by the double bond. It is noteworthy in passing that C(3) of **29** is located approximately over the double bond and accordingly experiences a pronounced shielding, δ4.6 compared with δ20.0 for C(3) of **28**; a broadly similar shift is found for C(2), C(4)[27].

III. ^{13}C CHEMICAL SHIFTS OF CYCLOPROPANES

The ^{13}C-NMR spectra of monosubstituted cyclopropanes were determined by the groups of Crecely[7] and Weiner[28] who treated the data as an ABB^{1}CC^{1}X spin system. The chemical shifts are given in Table 2.

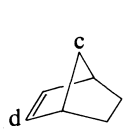
The α ^{13}C chemical shifts of the monosubstituted cyclopropanes correlate well with those of the corresponding methyl compound[28,29]. It is noted that C_α in iodocyclopropane[30] absorbs at rather high field; this is a manifestation of the not completely understood 'heavy atom effect'[31].

TABLE 2. ^{13}C chemical shifts (δ in ppm) of monosubstituted cyclopropanes

Substituent	$\delta C(1)$	$\delta C(2)$
H[a]	−2.9	−2.9
Cl[a]	27.3	8.9
Br[a]	13.9	8.9
I[a]	−20.2	10.3
COCl[a]	22.7	12.3
NH_2[a]	23.9	7.3
NH_2[b]	22.9	6.3
CN[b]	−4.1	6.5
COOH[b]	13.6	7.3
COPh[b]	16.1	10.4
COMe[b]	20.5	29.7
CH_2Ph[b]	19.9	4.9
Me[c]	5.3	6.0

[a] Data taken from Ref. 7 and transposed to TMS = 0 using $\delta CS_2 = 192.8$ ppm.
[b] Data taken from Ref. 28 and transposed to TMS = 0 using $\delta MeI = -20.7$ ppm.
[c] Data taken from Ref. 29 and transposed to TMS = 0 using $\delta cC_3H_6 = -2.9$ ppm.

As a continuation of studies of anisotropic shielding effects brought about by a cyclopropane ring, the large high-field shifts within the series **30–34** were examined by Tori and coworkers[32]. In **31**, C_c is shielded by 11.1 ppm with respect to the corresponding



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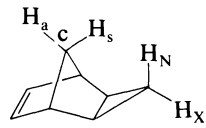
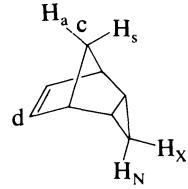


(31)



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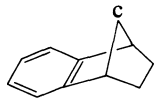

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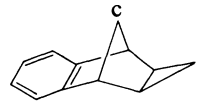
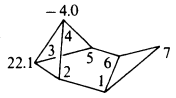


(34)

carbon C_c in norbornene, **30**. However C_c in **32** is deshielded by 15.2 ppm compared to C_c in **30**. In like manner C_d in the *endo* fused compound **32** absorbs 4.8 ppm upfield with respect to **30**, whereas in **31** C_d is deshielded by 5.9 ppm with respect to **30**. In the benzannelated compound **34** C_c absorbs at 37.1 ppm, 12.1 ppm upfield from the corresponding carbon in **33**. These sizeable shifts promoted a complementary examination of some ^1H-NMR spectra; however, in for example **30** and **32**, the chemical shifts of H_d are 5.93 and 5.64 ppm respectively. This implies that a steric compression shift is not of great

magnitude and accordingly, that direct interaction between H_d and H_N in **32** is not a prerequisite for a significant high field shift of the relevant ^{13}C absorption. Related phenomena were reported by Cheng and Stothers[33].

In an elegant choice of substrate Christl and Herbert studied the ^{13}C chemical shifts of tetracyclo[4.1.0.0^{2,4}.0^{3,5}]heptane (**35**) using both norbornene **30** and **36** as the basis for comparisons[34]. Inspection of **35** and **36** shows that both C(3) and C(4) experience high



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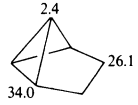

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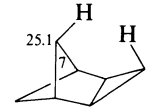

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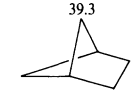
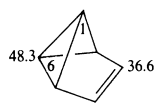


(38)

field shifts and that for the *anti* carbon C(3) is appreciably greater. The shifts can to some extent be visualized as normal γ effects[35].

Tricyclo[3.1.1.0^{2,4}]heptane (**37**) showed the ^{13}C chemical shifts indicated; with respect to the corresponding carbon in **38**, C(7) in **37** is shielded by ca. 14 ppm whereas C(6) in **37** is deshielded by 7 ppm by comparison with **38**[36]. The large shielding effect shown by C(7) in **37** is attributed to an enhanced interaction between the hydrogens specifically shown in **37**. The rather smaller *anti* effect in **37** is considered to have its origins in mixing of the highest occupied orbital of the C(2)–C(3) and C(3)–C(4) bond with the unoccupied cyclopropane Walsh orbital (a_2^1) in the prototype bicyclo[3.1.0]hexane, **11**, which is the origin of the



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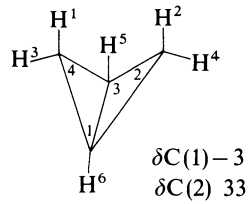

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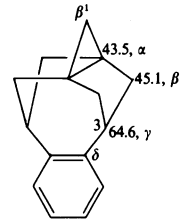
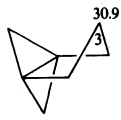


(41)

cyclopropane system in **31**, **32**, **34**, **35** and **37**. A weaker mixing in **37** than in **35** is considered to be the basis for the smaller deshielding of **37**.

Christl's group considered the ^{13}C spectrum of benzvalene (**39**) in which C(1) and C(6) absorb at rather low field for carbons of their type; this is paralleled by the ^1H absorptions of H_1 and H_6 at δ3.72. The ^{13}C chemical shift of the bridgehead carbons in bicyclobutanes are generally close to zero; in the specific case of bicyclo[1.1.0]butane (**40**), the chemical shift of C(1) is -3 ppm[36a,b] and there is a very large $\Delta\delta$ ca. 36 ppm between C(1) and C(2). The corresponding figure $\Delta\delta$[C(1)–C(5)] in bicyclo[3.1.0]hexane is 2.1 ppm and data collated from a number of bicyclo[n.1.0]alkanes do not reveal any systematic pattern[36a].

From an extensive set of data concerning annelation of cyclopropane rings to cyclopentanes, Christl and coworkers were able[37] to employ γ-*syn* shielding and γ-*anti* shielding correlations to assign structures. Four compounds which contain all four valencies within one hemisphere, 'inverted carbons', were considered; these were **41, 24, 42, 43** and their respective precursors without the 'cyclopropyl' methylene group viz: **44, 45, 11, 46**.



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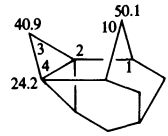

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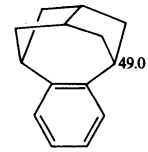

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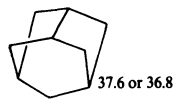

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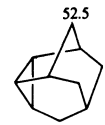
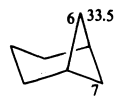


(46)

The *γ-anti* effect of 15.6 ppm at C(3) of **41** and the corresponding value of 16.8 or 17.6 ppm found for C(5) of **24** are 'normal' *γ-anti* effects of cyclopropanes and no additional consideration[38] of the 'inverted' carbons is required. Compound **42** is formally derived from **11**; on the basis of the *γ-anti* effect Christl and coworkers[37] assigned the absorption at 30.9 ppm in the ^{13}C-NMR spectrum of **42**[39] to C(3). In the conceptual formation of **43** from **46** the propellane is now in the boat form; accordingly C(1) in **43** now experiences an upfield shift with respect to **46**, though modest, 2.4 ppm.

In the consideration of **48**[40] with respect to **47**[41], two bicyclo[3.1.0]hexane moieties are included in the product, one in the boat and the other in the chair conformation. Thus whereas the *syn* carbon C(7) in **48** is shielded by 8.4 ppm with respect to **47**, a normal *anti*



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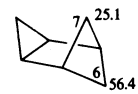
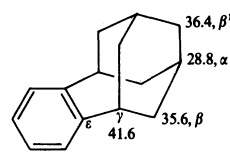


(48)

shift of appreciable magnitude, 22.9 ppm, is found for C(6). For both **41** and **24** similar sized downfield shifts of 23.0 and 25.9 ppm respectively were observed.



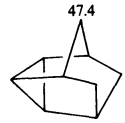
(49)

Duddeck and Klein also examined[40] the pair of compounds **41** and **49** of which the former has an 'inverted' carbon characterized by a long central bond formed by overlap of what are close to p orbitals. C_γ is shifted downfield by ca. 23 ppm with respect to **49**; a through-bonds transmission of the substituent effect is envisaged.

Rather smaller effects were noted in the γ shifts, 14.9 ppm, of **46** with respect to adamantane, **50**[37], and in **52** with respect to **51**, the figure is 11.7 ppm. Introduction of a

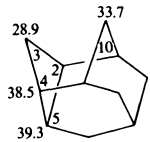
(50)

(51)



(52)

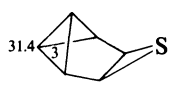
C(1)–C(4) bond into **47** to give **42** results in a downfield shift of 14.6 ppm for C(3). In **42** C(3) is *syn* to one cyclopropane ring and *anti* to the other, consequently C(3) here experiences a difference of the γ effects. The major influence is exerted by the chair effect since a net downfield shift is observed. In **43** corresponding deshielding of 16.4 ppm with respect to **53** is observed. The range of deshieldings of the C(3) carbons of



(53)

bicyclo[3.1.0]hexanes is 11.7–25.9 ppm, with the wide variety being attributed to the individual variations of geometry and strain. Indeed the γ shift associated with cyclopropane rings is at a maximum in systems that contain the built-in bicyclo[3.1.0]hexane moiety and the effect falls off markedly if the five-membered ring therein is enlarged[42]. If the size of the cyclopropane ring itself is increased the corresponding γ effects also become miniscule[43].

Although it is not within the scope of the review, the effect of annelation to give three-membered heterocycles, e.g. aziridines, oxiranes, thiiranes and thiirane *S*-oxides, was also investigated[37]. One particularly striking result might be mentioned; this concerns the ^{13}C-NMR spectrum of **55** with respect to **54**. The chemical shifts of C(3) in **55** and **54** are 31.4 and 8.4 ppm respectively, and the derived δ shift 'is without precedent'; on the other hand



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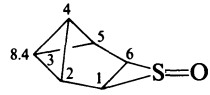
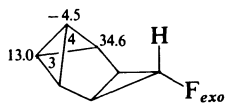


(55)

an analogous shielding effect of only 4.9 ppm is shown by C(4) of **55** with respect to the corresponding carbon of **54**. Similar though smaller effects were observed in **56** with respect to **35** and **36**; here it is thought that the role of the 7-*exo*-F is to transmit its substituent effect via a four-bond zigzag mechanism involving hyperconjugation, which is less stereochemically favourable in the epimer **57**[37].



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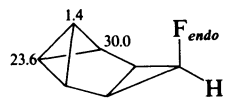


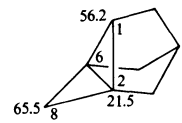
(57)

More recently the ^{13}C chemical shifts of **43** have been considered with respect to 2,4-methanoadamantane (**53**)[44]. In **43** the inverted carbons C(2), C(4) are shielded by 14.3 ppm with respect to the corresponding carbons of **53**. This finding which is apparently inconsistent with the slightly earlier reports of Duddeck and Klein[40] and Pincock and Fung[38] is reconciled by the consideration of three factors which are responsible for the shift differences. These are:

(1) deshielding brought about by rehybridization of the inverted carbons;
(2) the shielding effect of the new rings formed (see also Refs 18 and 45 for amplification of this); and
(3) a minor effect, a change in the influence of the neighbouring atoms brought about by formation of the new bond.

The outer carbons C(3) and C(5) are appreciably shielded as well in **43**. In order to be really satisfactory these three effects will need quantification or at least relative weighting. In the same molecule, **43**, C(10) was deshielded by ca. 16–17 ppm with respect to **53**; this agrees well with other relative shielding of carbon atoms situated across from the cyclopropane ring in a chair conformation[36, 38, 40].

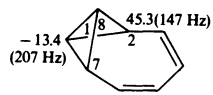
The same group[45] elegantly synthesized **58**, which possesses a strain energy ca. 15–20 kcal mol^{-1} greater than that of the parent [3.1.1]propellane, **42**, and determined the ^{13}C-NMR spectrum in C_6D_6/furan (1:1) at $-30°C$[45]. The ^{13}C spectrum of **58** includes rather low field absorptions for C(8), 65.5 ppm ($^1J_{CH}$ = 149, 171 Hz); C(1), 56.2 ppm ($^1J_{CH}$ = 189 Hz); C(2), C(6), 21.5 ppm. The bicyclobutane carbons C(1), C(2), C(6) are strongly



(58)

deshielded[45] now with respect to nortricyclene, **2**[46, 57]. This comparison is of a different type to that between **43** and **53**; an analogous comparison for **58** would be tricyclo[3.2.1.0^{3,7}]octane.

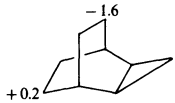
Benzvalene[48], **39**, on reduction gave tricyclo[3.1.0.0^{2,6}]hexane (**36**) whose ^{13}C chemical shifts are shown. In tricyclo[5.1.0.0^{2,8}]octa-3,5-diene (octavalene, **59**) the butadiene bridge widens the dihedral angle of the bicyclo[1.1.0]butane moiety from its normal value of ca. 122°. The ^{13}C-NMR spectrum shows C(1) and C(8) shifted upfield by ca. 10 ppm from their position in **41** to -13.4 ppm ($^1J_{CH}$ = 207 Hz) and C(2), C(7), now allylic, absorb at 45.3 ppm[49]. Rather strikingly C(1), C(8) of **59** are shielded by 61.7 ppm from the



(59)

position in benzvalene (**39**). This large shift difference is considered to provide support for the authors' proposal that chemical shifts are significantly affected by orbital interaction since the π^* oribitals of ethylene and 1,3-butadiene have different symmetry.

Kessler and coworkers[50] considered the influence of an annelated cyclopropane ring on a norbornane skeleton and on its homologue bicyclo[2.2.2]octane. The derived substitution effects shown in **60–62** show the small influence of a cyclopropane ring (or a double



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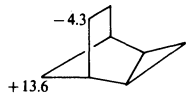

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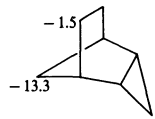
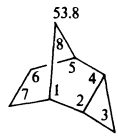


(62)

bond)[38] on the chemical shifts of the carbons of bicyclo[2.2.2]octanes. A bridge consisting of two unsaturated carbon atoms lacks the appropriate orbitals for it to interact with the antibonding asymmetric orbital of the three-membered ring; such is not the case with a methylene bridge.

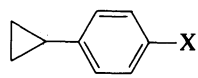
Introduction of an *endo*-cyclopropane ring into norbornane (**3**) results in a 13.6 ppm deshielding of the relevant carbon, C(8), in **63** with respect to C(7) in **3**[50]. This effect is



(63)

greater than that brought about by a double bond. The Walsh orbitals at C(2) and C(3) are practically parallel to the carbon–carbon bond-forming orbitals leading from C(8) of **63** to C(1) and C(5) (Figure 2) and so there is good scope for symmetry allowed overlap.

Roberts and coworkers[51] examined the substituent-induced shifts (SCS) of the α- and β-carbons of eleven 4-substituted cyclopropyl benzenes, **64**, at infinite dilution in $CDCl_3$.



(64)

Both C_α and C_β are deshielded by electron-withdrawing groups and shielded by electron-donating substituents. Representative data are given in Table 3; a larger range of SCS is

TABLE 3. ^{13}C chemical shifts of the cyclopropyl carbons (in ppm from TMS) of C_α and C_β in 4-substituted cyclopropylbenzenes

Substituent X	δC_α	δC_β
H	15.36	9.10
NH_2	14.61	8.20
Br	15.00	9.23
NO_2	15.86	10.98

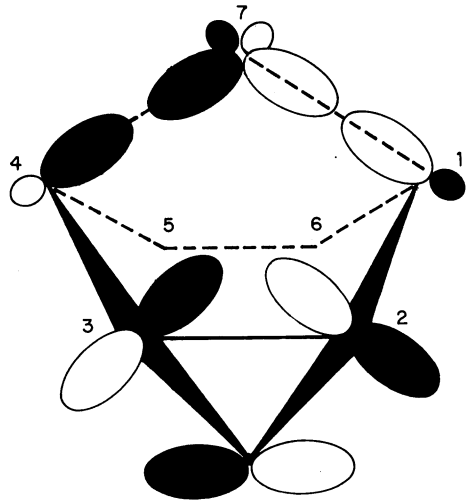
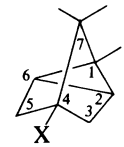


FIGURE 2

shown by the β-carbons. The SCS are discussed in terms of, e.g., the corresponding ethenyl and ethynyl systems. It was for instance found that the SCS (α) values are opposite in sense to those of, e.g., ethenylbenzenes and this was thought to be on account of the greater polarizability of the double and triple bonds than that of the cyclopropane ring, thereby permitting a significant contribution to the π inductive effects of substituent groups. The SCS (β) shifts of the cyclopropyl carbons are not completely understood.

The ^{13}C-NMR of nortricyclene, **2**, has been referred to, and Lippmaa[46] reported on a number of derivatives; the ^{13}C-NMR spectrum of quadricyclene, **65**, was assigned. The effect of 4-substituents *inter alia* on the cyclopropyl carbons C(2) and C(6) of 4-substituted tricyclenes (**66**) showed that there was an essentially linear dependence between δC(2) and

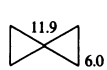
(65)



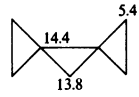
(66)

the electron-withdrawing ability of the substituent at C(4) such that for **66**, X = H, δC(4) = 20.6 and for X = NO_2, δC(4) = 18.8[52]. Although the range is fairly small, it is consistent and holds for a wide range of substituents. This trend has, in common with the carbonyl, the feature that electron-withdrawing substituents bring about progressive shielding[53].

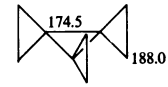
^{13}C chemical shifts of a number of diverse cyclopropane systems have been reported. It is not possible to catalogue all such structures here but a representative number of curiosities from spiropentane, **67**, through **69**[54], and the hexaspiroöctadecane (**70**) are



(**67**)



(**68**)



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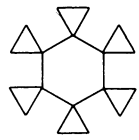
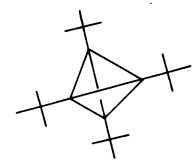


(**70**)



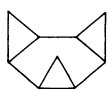
(**71**)

reported[55]. In **70** the quaternary carbons absorb at 26.2 ppm and of the methylene carbons the axials are, as is conventional, presumed to absorb at higher field, 1.3 ppm, with the equatorial carbons located downfield at 10.4 ppm.

One of the long sought after structures, tetrahedrane, was recently synthesized, as its tetra-*t*-butyl derivative **71**, and *inter alia* its ^{13}C-NMR spectrum is reported in different solvents in two papers[56]. In $CDCl_3$[56b] the ring carbons absorb at 9.27 ppm, the quaternary carbons bonded to methyl groups at 27.16 ppm and the methyl carbons at 31.78 ppm. Notably the quaternary carbon atom of the *t*-butyl group absorbs at higher field than those of the methyl group, on account of the bond between the *t*-butyl group and the neighbouring carbon possessing high s character; a similar situation obtains in di-*t*-butylacetylene. Taking into account the effect of the *t*-butyl group, it is predicted that the ^{13}C chemical shift of tetrahedrane would be ca. -15 ppm; a theoretically calculated value of -13.6 ppm was proposed[56b].

For completeness the coupling constants for **71** are given here, $^1J_{CH} = 125.2$; $^2J_{CH} = 3.9$; $^3J_{C(CH_3),H} = 4.7$ and $^3J_{C(ring),H} = 5.7$ Hz.

One molecule, as yet unsynthesized, but which may have an interesting ^{13}C- (and ^1H-) NMR spectrum is the *cis*-trishomobenzene (**72**); the *trans isomer* (**73**)[57] and the 'capped' homologue (**74**)[58] have both been synthesized but only the ^1H spectra have been reported.



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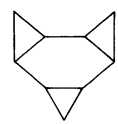
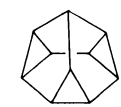


(**73**)



(**74**)

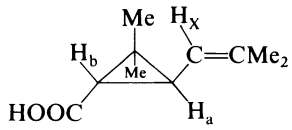
IV. PROTON–PROTON COUPLINGS OF CYCLOPROPANES

In cyclopropane rings three types of coupling constant are possible: (1) vicinal (*cis*), (2) vicinal (*trans*) and (3) geminal. The geometry of the cyclopropane ring indicates that the dihedral angle between *cis*-vicinal protons is 0° whereas that between *trans*-vicinal

protons[1] is 131–134° (see also Ref. 59). Mere consideration of these dihedral angles considered in accord with the precedent of coupling constants in acyclic systems (with the aid of the Karplus equation) leads to the expectation that in general $^3J_{HH,cis} > {}^3J_{HH,trans}$ and indeed this has been found to be so. Values of $^3J_{HH,trans}$ *mostly* lie within the range 3–5 Hz and those for $^3J_{HH,cis}$ are ca. 6–10 Hz; thus the two ranges do not overlap and so assignments can therefore be made with a large measure of confidence.

It should perhaps be pointed out that an early assignment of configuration[60] which had $^3J_{HH,trans} > {}^3J_{HH,cis}$ was subsequently reversed by the same group[61]. The greater magnitudes of the *cis*-vicinal coupling constant in cyclopropanes is thus the formal opposite of the situation that holds in olefins.

One of the early determinations[62] of vicinal coupling constants in cyclopropanes was that of the chrysanthemumic acids, *trans* acid (**75**) shown. For the ethyl esters in benzene,



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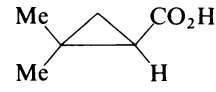


(76)

$J_{H_aH_b} = 5.5 \pm 0.1$ Hz in the case of the *trans* ester of **75** and for the *cis* epimer $J_{H_aH_b} = 8.7 \pm 0.2$ Hz.

As one of a number of examples Roberts and coworkers[1] found $^3J_{HH,cis} = 8.0 \pm 0.3$ Hz and $^3J_{HH,trans} = 5.6 \pm 0.3$ Hz in the case of **76**, with the geminal coupling $^2J_{HH} = 4.3 \pm 0.3$ Hz. At the same time Wiberg's group [63] reported *inter alia* that for **1**, X = Br, $^3J_{H^1H^2} = 7.3$ Hz and $^3J_{H^1H^4} = 3.9$ Hz; in this molecule $^2J_{HH} = -5.9$ Hz.

Scherr and Oliver[12] reported that the geminal coupling constants of a series of monosubstituted cyclopropanes are more sensitive to changes in molecular geometry, in particular slight variations in angles.

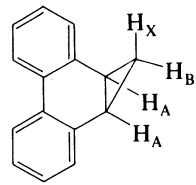
Subsequently, the coupling constants of twenty-two monosubstituted cyclopropanes were determined with great precision[13], though some of the substituents are rather similar. A small sample of the data is given in Table 4. From the data a plot of *cis* and *trans* coupling constants for the β-protons shows quite a good correlation.

TABLE 4. Proton–proton coupling constants in monosubstituted cyclopropanes

Substituent	$J_{H^1H^2}$	$J_{H^1H^4}$	$J_{H^2H^3}$	$J_{H^2H^4}$	$J_{H^2H^5}$	$J_{H^4H^5}$
Cl	7.02	3.59	10.55	−6.08	7.09	10.83
NO_2	7.01	3.42	10.09	−5.52	8.26	11.27
CN	8.47	5.09	9.42	−4.93	7.02	9.88
NH_2	6.60	3.52	9.77	−4.40	6.15	10.02
OAc	6.60	3.07	10.85	−6.26	7.45	11.77

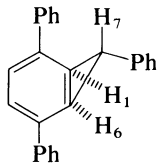
A complete analysis of the ^{1}H spectra of bromo- and iodocyclopropane was reported by Schrumpf and Lüttke[64].

From the A_2BX system which constituted the ^{1}H-NMR spectrum of **77** the chemical shifts were assigned, $H_A = 2.38$; $H_B = 1.45$; $H_X = -0.05$ ppm[65]. The coupling constants between these protons were $J_{H_AH_B(cis)} = +8.8$ Hz; $J_{H_AH_X(trans)} = 4.8$ Hz and $J_{H_BH_X(gem)} = -3.8$ Hz.



(77)

The relative magnitudes of the *cis*- and *trans*-vicinal proton–proton coupling constants have been decisive in assigning stereochemistry to **78**, the first simple norcaradiene with a proton at C(7). The *trans* relative configuration of H_1, H_6 and H_7 was indicated by the



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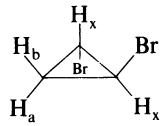

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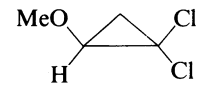


(80)

value $^3J_{H_1H_7} = 5.2$ Hz[66]. In the ^{1}H-NMR spectrum of a cyclopropane bearing two substituents, e.g. *trans*-dibromocyclopropane, **79**, the *cis*-vicinal coupling was $J_{H_aH_x} = 8$ Hz compared to the *trans* counterpart $J_{H_bH_x} = 2$ Hz[67].

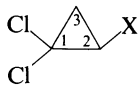
As one of a series of examples, it was found that in **80**, $J_{cis} = 7.90$ $J_{trans} = 5.28$ and $J_{gem} = 8.38$ Hz, and the authors make the point that in this environment proton–proton coupling constants are not greatly affected by the nature of the ring substituents[68]. However in a limited series of further substituted 1,1-dichlorocyclopropanes, **81**, Williamson and coworkers[69] did find significant variation. Selected data are shown in Table 5.

TABLE 5. Coupling constants (in Hz) of 2-X-1,1-dichlorocyclopropanes (**81**)

X	J_{cis}	J_{trans}	J_{gem}
OAc	8.0	5.4	−9.1
Br	9.4	6.6	−8.6
COOH	11.0	6.8	−6.8
$SiMe_3$	12.6	9.6	−4.9

Once the generality of the vicinal coupling constant sequence $J_{cis} > J_{trans}$ had become apparent it was possible for Wharton and Bair[70] to assign configuration to the two trimethylcyclopropanes; for the *trans* isomer (**82**) shown $^3J_{HH} = 6.0$ Hz and for the *cis* isomer $^3J_{HH} = 9.5$ Hz. In a variety of structures contained in thirty-five bicyclo[n.1.0]alkanes the vicinal proton–proton coupling constants between protons of the three-membered ring have values between 6.9 and 9.3 Hz when protons are *cis* and in the range 2.6–5.6 Hz when *trans*[19].

Geminal proton–proton coupling constants in cyclopropanes are usually found to be negative[1,63,67,71–73]. The values reported by Dauben and Wipke[19] had an average of



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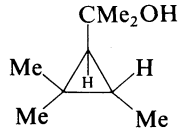

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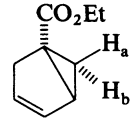


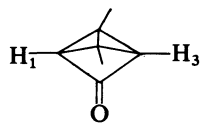
(83)

-4.51 Hz and ranged from -3.1 Hz for **83** to -5.6 Hz for cyclopropane[74]. The coupling constants may be perturbed by incorporation of the cylopropane ring into more strained systems, as in the case of bicyclo[1.1.0]butane (**40**)[75]. The proton–proton coupling constants are shown in Table 6, with long-range couplings also included. In **40** the geminal spin coupling is small both in respect to monosubstituted cyclopropanes and alkanes in general; the observed figure ca. 0.5 Hz is more akin to those found in alkenes of the type $>C=CH_2$.

TABLE 6. Proton–proton coupling constants (Hz) in **40**

Protons involved in coupling	J
H^3H^4	5.9 ± 0.2
H^3H^5, H^3H^6	2.9 ± 0.2
H^1H^3, H^2H^4	0.6/0.4
H^2H^3	0.4/0.6
H^5H^6	10.4
H^1H^5, H^2H^5	1.2 ± 0.2
H^1H^2	1.1

The long-range coupling $^4J_{H^3H^4}$ in **40** is noticeably large, 5.9 Hz. In the related but more strained molecule **84** the corresponding coupling $^4J_{H^1H^3} = 14$ Hz[75]. For the tetrachloro derivative **85** $^4J_{H^1H^3} = 0.75$ Hz and $^4J_{H^1H^4} = 1.15$ Hz[76]. In a partial analysis of the ^{1}H-NMR spectrum of **86** a long-range coupling $^4J_{H_aH_b} = 1.2$ Hz was found[77].



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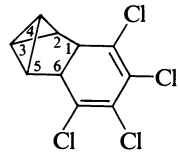

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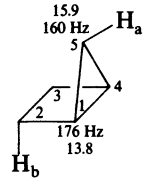

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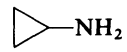
V. PROTON–^{13}C COUPLINGS OF CYCLOPROPANES

The coupling constant $^1J_{^{13}C-H}$ ($^1J_{CH}$) for cyclopropane was found to be 161 Hz by Muller and Pritchard[78a], a much higher value than found in cyclohexane (123 Hz) or cyclopentane (128 Hz) and rather close to that in benzene, (159 Hz). Crecely and coworkers found $^1J_{CH} = 160.5$ Hz in cyclopropane[79] (see also Refs 1 and 6). The large value obtained for cyclopropane reinforced earlier proposals that the C–H bonds in this molecule are close to

sp^2 hybridized. It was also proposed that J_{CH} is proportional to the fractional s character of the carbon atomic orbital used to form the bonding MO[80]. This led to the conclusion that the C–H bond in cyclopropane[72b] has ca. 32% s character. It is appropriate to state the results[79] of the calculations which suggest that the C–H orbital in cyclopropane is $sp^{2.28}$, and the C–C bond is rich in p character, $sp^{4.12}$. A reasonable correlation between $^1J_{CH}$ and the CCC interatomic angle was obtained with cyclopropane lying well on the line, and this despite the use of interatomic rather than interorbital angles[81].

Small variations in $^1J_{CH}$ were found in monosubstituted cyclopropanes, such that in cyclopropylamine (**87**), $^1J_{C(1)H} = 173$ Hz and $^1J_{C(2)H} = 161$ Hz[82]. Subsequently Crecely



(87)

and coworkers[79] found that in the series of monosubstituted cyclopropanes (**1**) $^1J_{C(3)H^5}$ varies from 160.45 (X = H) to 166.32 (X = COCl); a slightly larger coupling constant 166.99 Hz is observed when H is *trans* to the substituent.

The results of the carbon–proton coupling constants of some of these monosubstituted cyclopropanes are given in Table 7. Long-range carbon–proton coupling constants in monosubstituted cyclopropanes are such that they may be construed either as two bond or three bond coupling; in some cases the latter have been found to be larger. Cyclopropane itself shows $J_{C(1)H^2} = 2.55$ Hz; data for a number of monosubstituted derivatives are shown in Table 8.

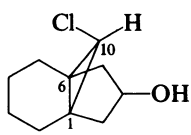
TABLE 7. Carbon–proton coupling constants in monosubstituted cyclopropanes (**1**) (in Hz)

Substituent	$J_{C(1)H^1}$	$J_{C(2)H^2}$	$J_{C(2)H^3}$
H	160.45	160.45	160.45
Cl	192.12	162.55	164.49
Br	192.62	162.28	164.98
	193.4	163.0	164.7[a]
I	187.65	162.65	165.44
	187.9	162.4	165.2[a]
COOH	170.10	164.53	165.88
NH_2	169.67	159.91	160.52

[a] Data from ref. 64.

TABLE 8. Long-range ^{13}C–H coupling constants for cyclopropanes (**1**) (in Hz)[7]

Substituent	$J_{C(1)H^2}$	$J_{C(1)H^3}$	$J_{C(2)H^1}$	$J_{C(2)H^4}$	$J_{C(2)H^5}$
H	−2.55	−2.55	−2.55	−2.55	−2.55
Cl	−1.15	−5.05	−0.55	−3.05	−2.75
I	−2.3	−5.5	−1.1	−2.75	−2.85
NH_2	−1.0	−4.0	+0.65	−2.9	−2.7



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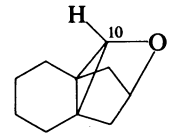


(89)

(90)

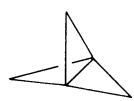
In **88** the magnitude of $^1J_{C(10)H}$ was 190 Hz and in the more highly strained compound **89**, albeit with a different substituent pattern, $^1J_{C(10)H}$ = 195 Hz[82,83]. In spirohexane, **90**, however, $^1J_{CH}$ for the cyclopropyl methylene moiety was 157.8 Hz.

The $^1J_{CH}$ (and $^1J_{CC}$) coupling constants in saturated hydrocarbons are most heavily influenced by the hybridization of the coupling carbon atoms via the Fermi contact term. Assuming that non-contact terms do not contribute significantly then it is possible to calculate the hybrid orbitals together with the interorbital angles from the relationship originally proposed by Muller and Pritchard[78b] in which the % s character of the carbon atomic orbital of a C–X bond is given by equation 3.

$$\% \text{ s} = 0.20\, J_{CH} \tag{3}$$

For cyclopropane this leads to hybridization indices CH, $sp^{2.12}$, CC, $sp^{4.58}$ and % s character CH, 0.3208, CC, 0.1792. The two interorbital angles in cyclopropane are calculated to be 118.2° (HCH) and 102.6° (CCC)[84].

The question of how the value of $^1J_{CH}$ is affected by location of the cyclopropane ring in more strained fused ring systems has been addressed by consideration of bicyclo[1.1.0]butane, **40**. Wiberg's group[85] showed that for this compound, $^1J_{C(2)H^2}$ = 152 Hz; $^1J_{C(2)H^4}$ = 170 Hz; and remarkably $^1J_{C(1)H^6}$ = 202 Hz; similar values were reported by Wüthrich and coworkers[36b]. The corresponding data for 1-cyano[1.1.0]butane (with $-C \equiv N$ replacing H^6 in **40**) were 170.4 Hz, 158.3 Hz and 207.8 Hz respectively; all coupling constants are slightly increased by the electron-withdrawing substituent[86]. Wiberg proposed[85] that the deformation of bond angles experienced by **40** results in a lower repulsive interaction and a C–H bond length that will decrease. The overlap integral between the C and H orbitals will increase and so then should $^1J_{CH}$. The 'ringalogue' **91** of

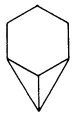


(91)

40 showed a value $^1J_{CH}$ = 165 Hz, in between the *exo* and *endo* coupling constants of **40** (also for **91**, δC(1) = 1.0 and δC(2) = 74.2 ppm)[87].

The carbon–proton coupling constants of a number of other bicyclo[1.1.0]butane derivatives have been reported; in general the magnitude of $^1J_{CH}$ within methylene groups of highly strained systems does not vary *greatly*. A number of cases for which data have been assembled will be cited. For **43** $^1J_{CH}$ for the non-equivalent protons of C(3), (δC(3) = 40.9), $^1J_{CH}$ = 149 and 171 Hz and for C(5) (δ64.4), $^1J_{CH}$ = 166 Hz[45]. The same group[45] has found $^1J_{CH}$ = 149 and 171 Hz for C(8) in **58** (δC(8) = 65.5) and for C(1) (δ56.2), $^1J_{CH}$ = 189 Hz.

Pincock and Fung reported a 'normal' value of $^1J_{CH}$ = 158 Hz for the methylene carbon C(9) of **24**[38]. A number of bicyclo[1.1.0]butane derivatives were investigated by Closs's group[88], in **92** $^1J_{C(1)H} = 200 \pm 1$ Hz; for **93** $^1J_{C(1)H} = 206 \pm 1$ Hz and in the still more



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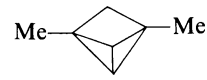

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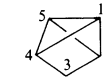
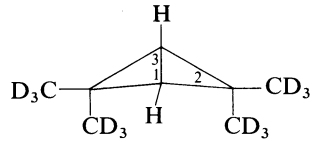


(95)

strained derivative **94** a still higher figure $^1J_{C(1)H} = 212 \pm 2$ Hz was reported. Rather later the corresponding coupling for the parent compound **95** was redetermined and found to be 210 Hz[89]. The β derivative labelled with deuterium as indicated and also at the bridgehead with ^{13}C was synthesized by Lüttke's group[90] and the values $^1J_{C(1)H} = +184.33 \pm 0.02$ and $^2J_{C(1)H} = -2.02 \pm 0.02$ Hz were determined; a large value $+12.22 \pm 0.02$ Hz was found for $^3J_{HH}$. This accurate investigation indicated a value of $^1J_{C(1)H}$ in **96** ca. 20 Hz smaller than in bicyclobutane. These data correspond to a 36.0% s character in



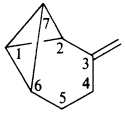
(96)

the C(1)–H bond of **96** compared to the figure of 41.0% in bicyclobutane. The low value of $^1J_{C(1)H}$ in **96** is rationalized in terms of an increase in the angle between the two three-membered rings; this is in accord with precedent.

For benzvalene (**39**) $^1J_{C(1)H} = 205.2$ Hz and $^2J_{C(2)H} = 168.8$ Hz[36a]; in the product of hydrogenation, **36**[34], the corresponding figures are 212 Hz and 34.0 Hz. In **35** the carbon–proton coupling constants reflect the environment of the carbons and the coupling constants were $^1J_{C(2)H} = 166$ Hz; $^1J_{C(3)H} = 209$ Hz, and $^1J_{C(4)H} = 215$ Hz; for the 'appended' cyclopropane ring $^1J_{C(1)H} = 171$ Hz and for the non-equivalent protons bonded to C(7), $^1J_{C(7)H} = 157$ and 162 Hz[34].

The butadiene bridge of octavalene (**59**) 'widens' the angle at the central carbon; the rather high field 'central' carbon shows $^1J_{C(1)H} = 207$ Hz and the much lower field allylic carbon C(2) has a 'normal' value $^1J_{C(2)H} = 147$ Hz[49]. From a comparison of the values of $^1J_{CH}$ in octavalene and **96** it appears that any correlation between the magnitude of $^1J_{CH}$ and the probable angle between the three-membered rings is not securely established.

A characteristically large value $^1J_{C(1)H} = {}^1J_{C(7)H} = 205$ Hz was found for the derivative



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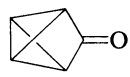

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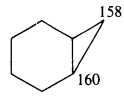

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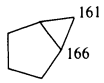

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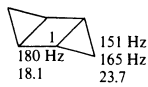


(101)

(102)

97[91a]; the couplings of C(2) and C(6) to the bonded protons were not reported. A very high coupling constant $^1J_{C(1)H} = 247$ Hz was found[91b] for the pentanone **98**.

In the bicyclo[n.1.0]alkanes **86**, **99** and **100**, the values of the proton–carbon coupling constants are as indicated[36a]. The introduction of further strain in **101** is instrumental in raising the coupling constants of $^1J_{C(1)H}$ to 180 Hz. In quadricyclene, **65**, it was shown that as a neat liquid $^1J_{CH}$ possesses an average value of 178.5 Hz, although the specific figure $^1J_{C(7)H} = 130$ Hz was reported[92]. A limited amount of data was reported for one-bond C–H couplings in nortricyclene (**2**)[93]. Prismane (**102**) derived interestingly from a photolysis carried out above room temperature, yielded a value of $^1J_{CH} = 179.7 \pm 2$ Hz in C_6D_6 (δ30.6)[94].

VI. ^{13}C–^{13}C COUPLINGS OF CYCLOPROPANES

Four reviews which include *inter alia* some data concerning carbon–carbon coupling constants in three-membered rings have appeared[95–98]. As with carbon–proton couplings, the carbon–carbon coupling is determined mainly by the Fermi contact term and calculations of these couplings rely principally on this term[99]. An impediment to the development of this subject is that, with the natural abundance of carbon 1.1%, the probability of two ^{13}C nuclei being present on adjacent carbons (for a $^1J_{CC}$ estimation) is ca. 1 in 10^4. Enrichment of at least one carbon can also involve troublesome synthetic procedures.

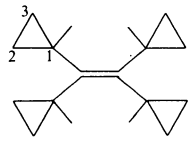
Recently the coupling constant $^1J_{CC} = 12.4$ Hz was determined for cyclopropane (also $^1J_{CH} = 160.4$ Hz, $^2J_{CH} = -2.6$ Hz) and the fraction of s character in the C–H bond was calculated to be 0.3208, and the fraction s character in the C–C bond was 0.1792[84]. The corresponding hybridization indices were estimated to be: CH bond, $sp^{2.12}$; CC bond, $sp^{4.58}$. The same calculations for cyclohexane, for which $^1J_{CC} = 32.7$ Hz gave the corresponding hybridization indices of $sp^{3.01}$ and $sp^{2.99}$.

Some other values of carbon–carbon coupling constants are given in Table 9. The data in Table 9 show that $^1J_{CC}$ in substituted cyclopropanes are proportional to J_{CH} in substituted methanes; it is also apparent that the coupling constants increase with increasing substituent electronegativity.

TABLE 9. $^1J_{CC}$ values (in Hz) in cyclopropane derivatives[100]

Substituent(s)	Bond	J
Br	C(1)–C(2)	13.3
I	C(1)–C(2)	12.9
1,1-di-Cl	C(1)–C(2)	15.5, 16.5[101]
Me	C(1)–C(2)	13.3
	C(1)–C_α	44.0, 43.4[102]
CO_2H	C(1)–C(2)	10.05
	C(1)–C_α	72.5
–CO– 	C(1)–C(2)	10.2
	C(1)–C_α	54.0
CN	C(1)–C(2)	10.9
	C(1)–C_α	77.9

Recently Lüttke and coworkers[103] have reported that the coupling constants within the cyclopropane ring of **103** are $^1J_{C(1)C(3)} = 10.8$ Hz; $^1J_{C(1)C(2)} = 16.7$ Hz; $^1J_{C(2)C(3)} = 13.0$ Hz.



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Robert's group[47] has also found that in nortricyclene (**2**), $^1J_{C(1)C(7)} = 40.4$ Hz (also $^1J_{C(3)C(4)} = 29.8$ Hz was determined) and in quadricyclene, **65**, $^1J_{C(1)C(2)} = 12.6$ Hz and $^1J_{C(1)C(7)} = 41.5$ Hz.

A relationship has been developed which, like its J_{CH} counterpart, relates J_{CC} to hybridization. This takes the form of equation 4[104].

$$J_{CC} = K_{CC}, s_i(j). s_j(i) \tag{4}$$

where $s_i(j)$ and $s_j(i)$ are the fractional s characters at each of the two respective bonded carbon atoms i and j[103,104]. K lies within the range 500–575 Hz. Sometimes s is expressed as a % and K has a value of ca. 0.0575. This equation indicates the importance of hybridization; electronic effects are also important in determining carbon–carbon coupling constants but in molecules of low polarity, e.g. hydrocarbons, they will not be of major importance.

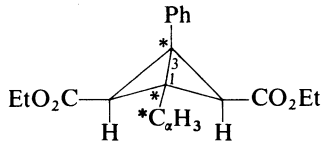
Grant and coworkers[104] have reported for **86**, $J_{C(4)C(5)} = 16.0$ Hz and $^1J_{C(1)C(2)} = 36.7 \pm 0.3$ Hz; from these data values of $s_1(2) = 0.29$ and $s_4(5) = 0.19$ were calculated. For **101** $J_{C(2)C(3)} = 18.2 \pm 0.2$ Hz, whence $s_2(3) = 0.22$, and in spiropentane, **65**, $J_{C(1)C(3)} = 20.2 \pm 0.2$ Hz and $s_1(3) = 0.15$.

This study also provided data on bicyclo[1.1.0]butane (**40**), for which $J_{C(1)C(2)} = 21.0 \pm 0.2$ Hz, $s_1(2) = 0.25$. From the value $^1J_{C(1)H} = 202$ Hz in **40**, the s hybridization in the bridgehead C–C bond is fixed at only 0.10. Consequently the C–C bond is derived essentially from p orbitals and is largely of π character

Schulman and Newton[105,106] employed the INDO method to develop a modified correlation (equation 5) between coupling constant and fractional s character.

$$J_{C_AC_B}(\text{in Hz}) = 0.0621(\%S_A)(\%S_B) - 10.2 \tag{5}$$

The authors presented the interesting result that both in benzvalene, **39**, and bicyclo[1.1.0]butane negative coupling constants between the bridgehead carbons were predicted. Experimental evidence for this proposal was provided by Pomerantz and coworkers[107,108] in a series of heteronuclear decoupling experiments with **104**. This triply



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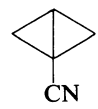

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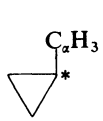
labelled material gave rise to $^1J_{C(1)C(3)} = -5.4 \pm 0.5$ Hz, $^1J_{C(1)C_\alpha} = 53.2 \pm 0.5$ Hz and $^2J_{C(3)C_\alpha} = -2.4 \pm 0.5$ Hz.

The previously studied **97** gave $^1J_{C(1)C(3)} = -17.49 \pm 0.02$ Hz; from the non-deuterated analogue of **96** Lüttke's group[90] also determined $^1J_{C(1)C(2)} = 23.06 \pm 0.12$ Hz; $^2J_{C(1)C_{exo}}$

$= 0.51 \pm 0.12$ Hz; $^2J_{C(1)C_{endo}} = 2.88 \pm 0.12$ Hz; $^1J_{C(2)C_{exo}} = 40.3 \pm 0.2$ Hz and $^1J_{C(2)C_{endo}} = 46.9 \pm 0.02$ Hz.

Lüttke proposed that substituent and/or steric influences were responsible for the large difference between $^1J_{C(1)C(3)}$ in **97** (−17.49 Hz) and **104** (−5.4 Hz). By analogy with **97** it appears that for **105** for which $^1J_{C(1)C(3)}$ is given as 16 Hz[86b], a negative sign is almost certainly in order. The value found for $^1J_{C(1)C(3)}$ in **97** is such that from any of the known equations relating J_{CC} to hybridization character, a negative value of $-s^2$ is found. This in turn leads to an imaginary value for the s character, which is naturally without physical meaning. It might be noted that Karabatsos and Orzech[109] albeit from a different standpoint and some time ago, were reluctant to accept the necessary correlation of s character with J values.

Some of the coupling constants of **95** have been disclosed[89]; these were $^1J_{C(1)C(2)} = 19.0$ Hz; $^1J_{C(2)C(3)} = 34.0$ Hz and $^1J_{C(1)C(3)} = 3.5$ Hz. A series of methylcyclopropanes **106–109** with one carbon enriched with ^{13}C was prepared[102] and the coupling constants



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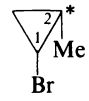

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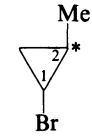

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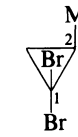

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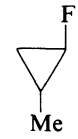
involving the enriched carbons are shown in Table 10. Inspection of the data reveals that *trans* substituents lead to a small but consistent increase of $J_{C(1)C(2)}$ whereas a *cis* substituent is almost without effect. In calculations of the value of $^1J_{C(1)C(2)}$ in the prototype

TABLE 10. Coupling constants (Hz) in ^{13}C enriched cyclopropanes

	$J_{C(1)C(2)}$	$J_{C(1)C_\alpha}$
106	13.3	43.4
107	13.4	45.1
108	14.7	45.2
109	14.4	43.2

molecules of *cis*- and *trans*-1-fluoro-2-methylcyclopropanes **110** and **111** values of 15.89 and 16.72 Hz were obtained. A comparable result was obtained for the 1,2-dimethylcyclopropanes. A calculation was then carried out using propyl fluoride and butane to assess

(110)



(111)

whether $^1J_{C(1)C(2)}$ in $MeCH_2CH_2F$ or $^1J_{C(2)C(3)}$ in butane was a function of dihedral angle. A shallow dependence was found in both cases with maxima and minima so positioned as to accord with the inequality $^1J_{CC(trans)} > {}^1J_{CC(cis)}$ in cyclopropanes.

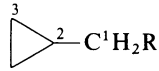
A quadratic expression was recently proposed by Pomerantz and Bittner[110] to express the dependence of $^1J_{CC}$ with the bond angle CCC by analogy with one proposed earlier for $^1J_{CH}$ values[111]. A levelling off of $^1J_{CC}$ values was observed for the angles in excess of ca. 120° and a steep drop down to cyclopropanes $^1J_{CC} = 13$ Hz, $\theta = 60°$; the equation proposed took the form of equation 6.

$$^1J_{CC} = -49.04 + 1.377\theta - 0.005662\theta^2 \quad (6)$$

In turn, a modification of equation 6 was proposed[112]. Whereas in $^1J_{CH}$ couplings only one pathway is permissible, in cyclic (and especially small cyclic) molecules two pathways are possible in principle for J_{CC} couplings[113]. From non-cyclopropane data a relationship is given that on extrapolation to 60° leads to $^1J_{CC} = 24.85$ Hz; subtraction of a stated two-bond contribution of ca. −12 Hz gave a result in accord with experiment.

Earlier, Klessinger and Stöcker[114] had come to a similar conclusion concerning formal $^1J_{CC}$ couplings in cyclopropane (and cyclobutane). These were interpreted as $^{1+2}J_{CC}$ and with the aid of their SCPT calculations in the INDO approximation on variation of $^2J_{CC}$ as a function of dihedral angle in propane, Klessinger and Stöcker were able to estimate $^2J_{CC} = -15$ Hz. With $^1J_{CC} = 23$ Hz the value $^{1+2}J_{CC} = 8$ Hz is in reasonable agreement with the experimental value of 13.3 Hz. Reasonable agreement was found by these authors for other small ring systems. The observed coupling between any two adjacent carbons in cyclopropane can be construed as the sum of a one-bond coupling and a two-bond coupling. To this sum the designation ^{1+2}J is frequently given; analogously it is possible to refer to ^{1+3}J in cyclobutanes.

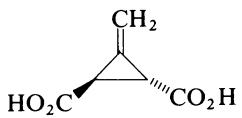
For **112** Stöcker found that $^1J_{C(1)C(2)} = 47.8$ Hz compared to a corresponding value of 43.4 Hz for **113**[115]. This finding is in accord with other data in which ΔJ drops to 3.1 Hz for the ethanol/ethane pair.



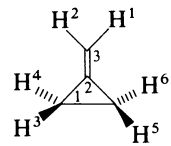
(**112**, R = OH)
(**113**, R = H)

VII. METHYLENECYCLOPROPANES, VINYLCYCLOPROPANES AND DERIVATIVES

The first methylenecyclopropane to be investigated was Feist's acid **114** by three groups[116], closely followed by studies on the parent compound **115** by both ^{1}H-NMR spectrum in a nematic phase[117] and ^{13}C-NMR spectroscopy[118].

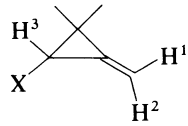


(**114**)



(**115**)

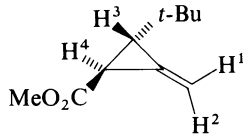
In **116** the cisoid coupling $J_{H^1H^3} = -1.79$ Hz compares with $J_{H^2H^3} = -2.55$ Hz for the transoid. The bromo derivative **117** shows more positive values for both couplings,



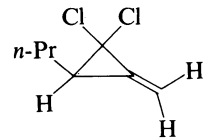
(**116**, X = H)
(**117**, X = Br)

−1.22 and −1.98 Hz respectively[119,120]. (A definition of cisoid and transoid coupling constants is given in Ref. 121.) In the case of **115** the cisoid (1.7 Hz) and transoid (2.6 Hz) couplings have also been reported[122].

In *inter alia* the *t*-butyl substituted compound **118**, the cisoid allylic couplings constants to H^3, 2.3 Hz and that to H^4, 1.9 Hz together with the transoid counterparts to H^3, 2.6 Hz and to H^4, 2.4 Hz indicated a slight variation of the coupling constant with substituent electronegativity[123]. In **119** the cisoid and transoid coupling constants were 2.4 and 2.8 Hz



(**118**)



(**119**)

respectively[124]. A review of allylic coupling has been published[121]. For **115** the NMR parameters are given in Table 11. On the basis that C(2) and C(3) are sp and sp^2 hybridized and with $K = 575$, then the calculated $J = 575 \cdot \frac{1}{2} \cdot \frac{1}{3} = 95.8$ Hz is in good agreement with the experimental value of 95.2 Hz.

TABLE 11. NMR parameters of methylenecyclopropane (**115**)[119,125] (δ in ppm, J in Hz)

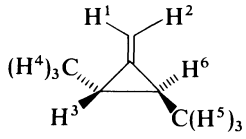
$\delta H^1, H^2$ 5.469	$^2J_{H^1H^2}$	1.31 Hz
	$^2J_{H^3H^4}$	−8.30 Hz
δH^3–H^6 1.026	$^3J_{H^3H^5}$	9.94
	$^3J_{H^3H^6}$	5.78
	$^4J_{H^1H^3\,(cisoid)}$	−1.74
	$J_{H^1H^5\,(transoid)}$	−2.48
$\delta C(1)$ 2.832, 3.0[126]	$^1J_{HC(1)}$	161.58
$\delta C(2)$ 131.0	$^2J_{HC(1)}$	−2.99
$\delta C(3)$ 103.5	$^3J_{HC(1)cis}$	4.35
	$^3J_{HC(1)trans}$	9.82
	$J_{C(1)C(2)}$	23.2
	$J_{C(2)C(3)}$	95.2

The NMR parameters of *trans*-2,3-dimethylmethylenecyclopropane, **120**, are shown in Table 12. It is noteworthy that in the *cis* isomer of **120** $J_{H^3H^5} = 10.11$ Hz, appreciably larger than in the *trans* isomer.

TABLE 12. NMR parameters of **120** in C_6D_6 (δ in ppm, J in Hz)

$\delta H^1, H^2$	5.511	$^2J_{H^1H^2}$	1.25
$\delta H^3, H^6$	1.012	$^4J_{H^1H^3}$	−1.75
$\delta H^4, H^5$ (Me)	1.165	$^4J_{H^2H^3}$	−2.25
		$^3J_{H^3H^6}$	4.45
		$^3J_{H^3H^4}$	6.25
		$^4J_{H^4H^6}$	−0.35
		$^5J_{H^1H^4}$	0.1
		$^5J_{H^2H^4}$	0.35
		$^5J_{H^4H^5}$	0

Newsoroff and Sternhell[126] examined the ^{1}H-NMR spectra of a number of methylenecyclopropanes among them **121** for which $J_{H^1H^3} = 1.95$ Hz and $J_{H^2H^3} = 1.20$ Hz and



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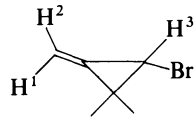
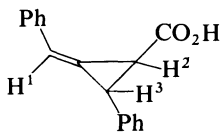


(121)

the isomers **122** and **123**. In **122**, $J_{H^1H^2} = 2.30$, $J_{H^1H^3} = 2.20$ and $J_{H^2H^3} = 3.6$ Hz and for **123** $J_{H^1H^2} = 1.85$, $J_{H^1H^3} = 2.25$ Hz, $J_{H^2H^3} = 3.5$ Hz. The authors state that in general ^4J transoid > ^4J cisoid in the case of alkylidene groups exocyclic to three-membered rings[126]; a number of references to earlier work within this category are cited.



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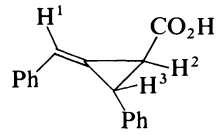
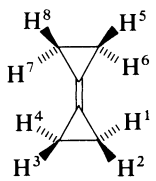


(123)

In the case of Feist's acid **114** the possibility was admitted that the large value $^4J = 2.63$ Hz was due to the electronic nature of the cyclopropane ring which imparts an allene type character to the molecule[127].

In the substituted olefin **124**, slightly more deshielded protons were noted δ1.13 (s, CCl_4)[128] or 1.12[129]. Both direct and indirect couplings were observed[130] for **124** as a



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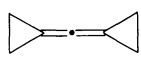

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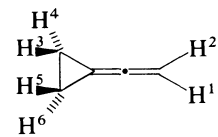


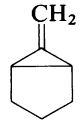
(126)

0.1 M solution in the nematic phase Eastman Kodak 12–100°C. The spectral analysis was insensitive to the value of $J_{H^1H^2}$ (taken as -7.0 Hz) used in the computation. The indirect couplings (in Hz) derived from this study were:

$J_{H^1H^3}$	6.03 ± 0.32
$J_{H^1H^4}$	8.37 ± 0.38
$J_{H^1H^5}$	2.41 ± 0.27
$J_{H^1H^6}$	1.82 ± 0.30
$J_{H^1H^7}$	2.81 ± 0.27

Slightly later Kopp and Hanack[131] noted that **125** in CCl_4 gave a singlet at 1.5 ppm. The simpler allene, **126**, in CCl_4 showed two absorptions in a relative ratio 2:1 at δ 1.40 and 4.65 with a coupling $^5J = 4$ Hz over five bonds that is noteworthy. Courtieu's group[132] examined the ^{1}H-NMR spectrum of **126** in the nematic phase Eastman Kodak 12–100°C at 400 MHz and elucidated the following coupling constants: $J_{H^1H^3} = 4.5 \pm 1.6$; $J_{H^1H^4} = 3.6 \pm 1.6$; $J_{H^3H^6} = 6.2 \pm 0.4$; $J_{H^3H^5} = 9.6 \pm 0.6$ Hz. Spectral analysis was virtually independent of the values of $J_{H^1H^2}$ and $J_{H^3H^4}$, which could not be determined; accordingly they were assigned values of 1.3 and -7.0 Hz respectively. A tabulation of direct coupling constants D was also presented.

In the above study[132] the assumed values were taken from earlier work with methylenecyclopropane by the same group[133] using both the above nematic phase and also Merck 7A-10-80°C. This work revealed that non-trivial differences in geometry, in particular a widening of the vinylic HCH angle by ca. 8°, could occur in the nematic phase.



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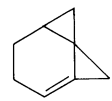

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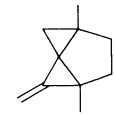

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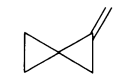
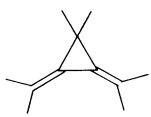


(130)

The indirect coupling constants for **115** (400 MHz, Eastman Kodak 12–100 °C) were $J_{H^1H^2} = 1.5 \pm 0.4$; $J_{H^1H^3} = -1.81 \pm 1$; $J_{H^1H^5} = -2.0 \pm 1.7$; $J_{H^3H^4} = -7.0$; $J_{H^3H^5} = 10.0 \pm 0.4$ and $J_{H^3H^6} = 5.8 \pm 0.3$ Hz; direct couplings were again cited.

In **127** only the broad features were apparent in the ^{1}H-NMR spectrum, δ 5.18 (s, vinyl H) and the remaining eight protons absorbed at δ 1.67 (m)[134]. In the interesting compounds **128–130**[135–137] specific attribution of the absorptions was not given.

The two unusual compounds, **131** and **132**, were synthesized by Bleiholder and Shechter[138]. In the former compound the ring methyl protons absorb at δ 1.18 and the



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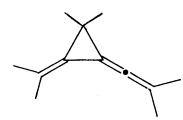

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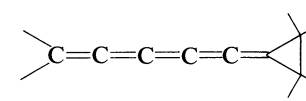


(133)

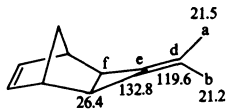
isopropylidene protons at 1.80 and 1.87 ppm. The allenic compound **132** showed absorptions for the protons on methyl groups bonded to the ring, olefinic and allenic carbons, at 1.30, 1.78 and 1.85 ppm respectively.

The compound **133**, a carbene addition product, showed two singlets at δ 1.80 and 1.17 in the ratio 1:2[139]. The ^{13}C spectrum which was not assigned showed absorptions at 163.5, 121.1, 116.2, 111.7, 28.3, 24.6 and 21.1 ppm.

TABLE 13. ^{13}C chemical shifts of **134** and **135**

	134	**135**
C_a	21.5	21.3
C_b	21.2	21.2
C_c	—	97.4
C_d	119.6	186.3
C_e	132.8	92.7
C_f	26.4 ($^1J_{CH}$ 173 Hz)	29.3 ($^1J_{CH}$ 171 Hz)

The ^{13}C chemical shifts of the methylenecyclopropane **134** (original lettering preserved) and its allenic counterpart **135** are shown in Table 13. These data are of interest in that for **135** C_e absorbs upfield from C_e in **134**[140].



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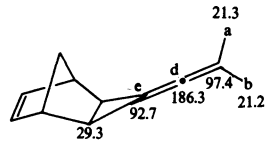


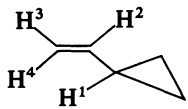
(135)

For **136** at $-80°C$ the ^1H-NMR spectrum (270 MHz) showed δ 1.99 (bridgehead methine H, br, s) and δ 1.74 (allylic methyl, s)[141]. At $-63°C$ in $CDCl_3$–$CFCl_3$ (1:1 v/v), the

(136)

vinyl carbons absorbed at 126.50 and 116.28 ppm and C(7) at 22.13 ppm ($^1J_{CH}$, 125.77 Hz)[141]. The s character in the bridgehead C–H bond is calculated to be ca. 35%.

The ^1H-NMR spectrum of vinylcyclopropane (**137**) was observed between -60 and $+70°C$ in CS_2 and CCl_4, the latter of which induced a downfield shift of ca. 0.02 ppm at a given temperature. Three parameters, δ_2, δ_4, and $J_{H^1H^2}$ are significantly temperature dependent and δ_2 and δ_4 show a linear correlation with $J_{H^1H^2}$ and this is consistent with a common origin for these effects, viz., rotation about a carbon–carbon single bond. The s-

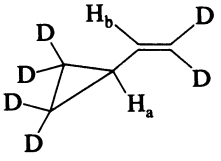


(137)

trans form, shown in **137**, particular to which is a dihedral angle of 180° between H^1 and H^2, is taken to be the low energy conformation[142].

From a graphical method the energy separation between the s-*trans* and s-*cis* forms was found to be ca. 0.8 kcal mol^{-1}. The anisotropic diamagnetic polarizability of the cyclopropane ring was estimated to be ca 60×10^{-30} cm^3.

The s-*trans* conformation was shown to be favoured from a study of the temperature dependence of the vicinal coupling, $J_{H_aH_b}$ in the deuterated derivative, **138**[143]. At −30°C $J_{H_aH_b}$ (obs) = 9.13 Hz. The *trans* conformer was more stable by ca 1.1 ± 0.2 kcal mol^{-1}. A threefold rotation barrier was indicated in later work[144].



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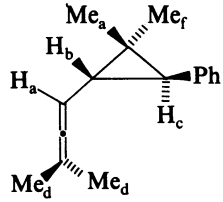

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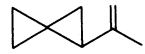
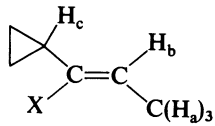


(140)

Analysis of the ^{1}H-NMR spectrum of **139** gave the coupling constants, $J_{H_aH_b}$ = 6.6 Hz, $J_{H_bH_c}$ = 5.6 Hz and $J_{H_aH_d}$ = 3.0 Hz; H_b and H_c absorb respectively at 1.54 and 1.77 ppm[145].

^{1}H-NMR data on a number of diversely substituted derivatives of **140** have been reported[146].

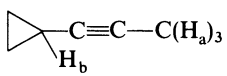
A number of long-range proton–proton couplings within the compounds **141** and **142** have been reported from analysis of the 200 MHz spectra[147]. In both geometric isomers



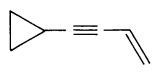
(141) X = I
(142) X = OAc

$^4J_{H_bH_c}$ = 1.2 Hz and H_c absorbs in the range δ 1.2–1.75. A rather smaller coupling $^4J_{H_bH_c}$ = 0.8 Hz was determined for the enol acetate **142** (X = OAc). The homoallylic coupling constants, $^5J_{H_aH_c}$ = 0.7 Hz for **142** (X = I) and 1.2 Hz for **141** are in accord with earlier cited work on related compounds. The effect on the chemical shift of a vinyl proton brought about by the introduction of a *cis* or *trans* cyclopropyl ring has been found to be rather small[147, 148].

In the alkyne **143**, derived from **141**, there is also a long-range coupling $^5J_{H_aH_b}$ = 1.38 Hz; H_b absorbs between 0.75 and 1.35 ppm and the methylene protons absorb in the range 0.4–0.75 ppm.

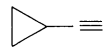


(143)



(144)

Hanack's group has reported on **144** in which no proton–proton couplings were readily discernible[149].

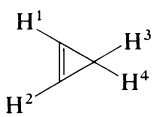


(145)

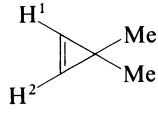
Ethynylcyclopropane, **145**, was the prototype of a series of methyl and bromo derivatives employed in a ^{13}C chemical shift study[150]. The ^{13}C chemical shifts were C(1) 2.4; C(2), C(3), 11.0; C(4), 90.4; C(5), 66.9 ppm and the ^{1}H shifts were reported by Schoberth and Hanack[151].

VIII. CYCLOPROPENES

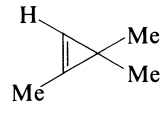
The ^{1}H-NMR spectrum of cyclopropene **146** was initially reported by Wiberg and Nist[152] who observed δ 2.99 (t), 0.98 (t) (15% solution in CCl_4) and $J_{H^1H^3} = 1.8$ Hz (see also Ref. 153). Closs and Closs reported the ^{1}H chemical shifts of a number of cyclopropenes, exemplified by **147**, δ 0.93 (t) and 7.00 (sept) and **148**, δ 6.65 (m); 2.00 (d) and 1.06 (d)[154–156].



(146)

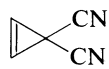


(147)



(148)

The 90 MHz ^{1}H-NMR spectrum of cyclopropene, **146** was analyzed fully using neat substrate, at $-60°C$. The chemical shifts were $\delta H^1 = 7.06$, $\delta H^3 = 0.93$ ppm; from the ^{13}C satellites of the vinyl proton the values $J_{H^1H^2} = 1.3$ Hz and $J_{H^1H^3} = 1.75$ Hz were determined[157]. The spectral analysis assumed that $J_{H^3H^4} = -12.00$ Hz. The value of $J_{H^1H^2}$ cited above forms part of a sequence whose next three members are cyclobutene, 2.85 Hz; cyclopentene, 5.1 Hz and cyclohexene, 8.8 Hz.

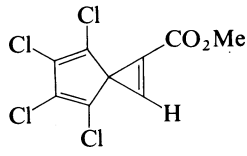


(149)

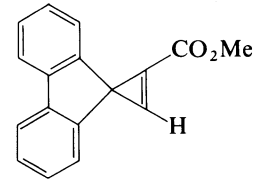
At about the same time Ciganek[158] synthesized **149**, in which the vinyl protons absorb at δ 7.22; in addition $^{1}J_{CH} = 225$ Hz (51% s character in the C–H bond). The corresponding coupling constants for **147** were 200 Hz (44% s character)[155] and 226 Hz (45% s character)[157]. In the more heavily substituted derivative **150**, the value of $^{1}J_{C(2)H} = 248$ Hz (43.2% s character) was determined; here the figure in parenthesis derives from a modified formula[159].

$$\% \text{ s} = {}^{1}J_{CH}/6.9 + 7.37$$

A corresponding figure $^{1}J_{C(2)H} = 236.8$ Hz was reported for the 9-fluorenyl analogue **151**[160].



(150)



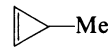
(151)

The ^{13}C spectrum of cyclopropene determined by Günther and Seel[161] showed C(1), 108.7 ppm ($^1J_{CH}$ = 228.2 Hz); C(2), 2.3 ppm ($^1J_{CH}$ = 167.0 Hz). The value of 228.2 Hz is slightly greater than that determined from the satellites of the ^1H-NMR spectrum.

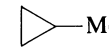
With respect to the corresponding carbons in cyclobutene, C(1) in cyclopropene is shielded by 28.5 ppm and C(3) by 29.1 ppm; these values are rather similar to that, 25.9 ppm, of the corresponding cyclopropane–cyclobutane shift. Further, the methylene carbon in cyclopropene is deshielded by 4.9 ppm with respect to cyclopropane.

In **152** the methyl carbon δ 12.5 ($^1J_{CH}$ = 129.0 Hz) is shielded with respect to that in **153** δ 23.6 ($^1J_{CH}$ = 124.5 ppm) or indeed **154**, δ 19.9 ($^1J_{CH}$ = 126.1 Hz). This observation

(152)



(153)

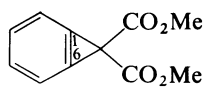


(154)

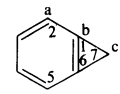
stands in contrast to open chain olefins in which deshielding of unhindered methyl carbons at sp^2 hybridized centres is normally encountered, but accords both with 1-phenylpropyne δ Me = 4.9, and a shielding of ca. 11 ppm experienced by methylene carbons bonded to sp hybridized centres.

A similarity is seen to exist between the formal double bond of cyclopropene and the carbon–carbon bond in an alkyne; in this context the value of $^1J_{CH}$ = 129.0 Hz for the coupling constant within the methyl group of **152** (see above) is slightly enhanced in the corresponding coupling, 132 Hz, in propyne. Indeed, the prediction was made by Walsh[162] and noted by Closs[163], that the properties of cyclopropenes would be intermediate between those of unstrained alkenes and alkynes.

Subsequently, Dürr's group examined the ^{13}C-NMR spectra of a number of cyclopropenes and also benzocyclopropenes[164], in particular the ^{13}C chemical shifts of **155**, δ C(1),



(155)



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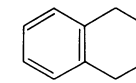
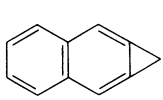


(157)

C(6) = 12.84, $^3J_{CH}$ = 4.4 Hz; δ C(7) = 45.0. In benzocyclopropene itself (**156**), the carbons absorb at higher field[165], thus δ C(7) = 18.4 $^1J_{C(7)H}$ = 170 Hz; also δ C(1) = 125.4. The chemical shift for C(7) is characteristic of ring strain, progressive homologation results in a lowering of the value of $^1J_{CH}$ for the methylene groups until a limit of 126 Hz is reached for **157**.

The ^1H-NMR chemical shift of **156** had previously been reported; in CCl_4 δ H(7) = 3.11, $^1J_{CH}$ = 178 ± 2 Hz[166].

The methylene protons of **158** absorb at ca. δ 3.4[167]; for **159** Ippen and Vogel found δ 7.59 and 3.52 in the ^{1}H-NMR spectrum and the methylene carbons absorbed at δ 19.9 with $^1J_{CH} = 170$ Hz[168]. Slightly later Vogel's group[169] reported that the methylene protons of the less stable compound **160** absorb at δ 3.42(s) at -20°C in CCl_4.



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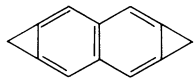

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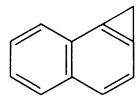
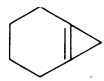


(160)

From the ^{13}C-NMR spectrum of **156**, Günther and Herrig determined $J_{C(1)C(2)} = 87.1$ and $J_{C(1)C(7)} = 20.8$ Hz. By means of the equation $J_{CC} = 550 s_i s_j$ where the symbols have the meaning previously ascribed, values of $J_{C(1)C(2)} = 91.7$ and $J_{C(1)C(7)} = 22.9$ Hz were estimated[170]. Also reported was $^1J_{C(7)H} = 170$ Hz. It is estimated that there exists 3.6% more s character in the CH_2 bonds of **156** with respect to those of cyclopropane, and accordingly 1.8% less s character in each CC single bond of **156**.

NMR spectral data have been reported on a number of diverse cyclopropenes and these include the highly strained (ca. 90 kcal mol^{-1}) spiropentene **161** in which the methylene

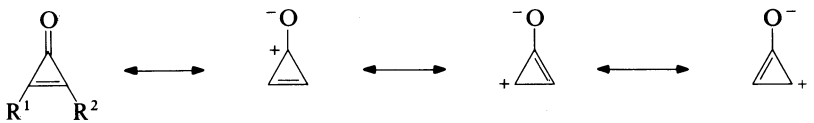
(161)



(162)

and vinyl protons are split by 1.5 Hz; the vinyl and methylene protons absorb at δ 7.10 and 0.58 respectively. The ^{13}C chemical shifts were C(1), C(2), 114.7; C(3), 16.8 and C(4), C(5), 4.1 ppm[171]. Closs's group synthesized **162** and the ^{1}H-NMR spectrum at -60°C (the compound dimerizes above -20 °C) showed signals at 1.21 (s, 6H); 1.7 (m, 4H) and 2.3 (m, 4H)[172].

The ^{13}C-NMR spectrum of cyclpropenone (**163**) was reported by Breslow's group[173]. The olefinic carbons absorb at δ 158.3 with C(3) at rather high field for a carbonyl carbon. In **164** slight shielding of the olefinic carbons was observed, δ 148.3, with C(3) absorbing at



(163, R = H)
(164, R = Ph)

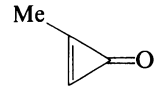
(165) **(166)** **(167)**

δ 155.9. In the case of **163** a high dipole moment, $\mu = 4.39$D was reported and, in addition, the charges on the carbon atoms were calculated to be, C(1), C(2) -0.287e and on C(3) $+0.436$e. The structure of cyclopropenone contains contributions from **163**, **165–167** although significant weighting is given to **165**, the other structures still have relevance.

For cyclopropene $\Delta\chi(10^{-6}$ erg/G^2 mol$) = -17.0$ compared to a similar value of -17.8 for cyclopropenone. The lack of any significant increase in $\Delta\chi$ for cyclopropenone should be considered in the light of the estimate[174] that delocalization of only two π electrons over the small ring induces deshielding effects brought about by the ring current

which are ca. one-quarter of those in benzene. In addition a carbonyl group could well act to suppress the diamagnetic anisotropy.

The proton chemical shifts of cyclopropenone in aqueous solution had been reported as δ 9.0 with $^1J_{CH} = 230$ Hz[175], and broadly similar values have been found for kindred compounds[176]. Thus for **168**, in the ^{1}H-NMR spectrum δ 8.66 (1H), 2.40 (3H) and $^1J_{CH}$

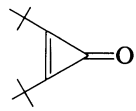


(168)

$= 213 \pm 4$ Hz again indicated a large % s contribution to the carbon hybrid orbital; in dimethylcyclopropenone the methyl protons absorbed at δ 2.25.

Breslow and Oda subsequently re-examined the coupling constants of cyclopropenone in some detail. In $CHCl_3$ they found $J_{CH} = 217 \pm 1$ Hz, $J_{HH} = 3.9 \pm 0$ Hz. In concentrated sulphuric acid protonation on oxygen is reflected by a change in $^1J_{CH}$ to 250 $\pm$ 1 Hz and J_{HH} to 1.3 ± 1 Hz[177].

The proton NMR spectrum of di-*t*-butylcyclopropenone (**169**) in $CDCl_3$ gave a singlet



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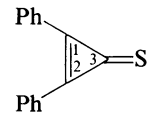
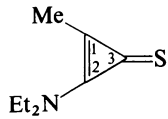


(170)

at δ 1.34[178] and the ^{13}C-NMR spectrum of the olefinic and carbonyl carbons were respectively 164.6 and 159.4 ppm[179, 180].

The extension from cyclopropenones to cyclopropenthiones was made by Dehmlov and coworkers[180] who reported ^{13}C chemical shifts C(1), C(2) 153.4 and C(3) 177.6 ppm for **170**; the corresponding shifts for diphenylcyclopropenone are 148.4 and 155.8 ppm. It is seen that the carbon bonded to sulphur absorbs at appreciably lower field than the corresponding carbonyl carbon and indeed this behaviour is characteristic of a thioketone–ketone pair.

More recently the cyclopropenthione **171** which contains a strongly electron-releasing diethylamino group was shown to have absorptions at 151.76 and 128.56 ppm for C(1) and



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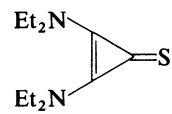


(172)

C(2), C(3) resonated at 161.27 ppm and the methyl carbon at 9.43 ppm[181]. The same group reported that C(1), C(2) and C(3) of the symmetrical molecule **172** absorbed at 133.32 and 133.58 ppm respectively.

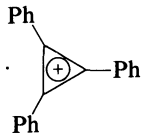
Fluorinated cyclopropenes are mentioned in the section concerning fluorinated derivatives.

IX. CYCLOPROPENIUM IONS

This section is confined to cyclopropenium ions. Cyclopropylcarbinyl cations are not considered although these ions are of interest on two counts: (1) the relationship with the bicyclobutonium ion, (2) their bisected geometry in certain cases (which has relevance to the conformation of nitrocyclopropane[182]) as they have recently been reviewed[183].

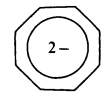
The proton chemical shift of the cyclopropenium carbocation **173** was reported as δ 11.1–11.2 in either sulphur dioxide, nitromethane or acetonitrile; two coupling constants were observed, $^1J_{CH} = 265 \pm 1$ Hz and $^2J_{CCH} = 50$ Hz[184]. At about the same time Olah's group[185] reported the ^{13}C spectrum of **173**, δ 176.5 and $^1J_{CH} = 262$ Hz. The chemical shift of the ring carbons of triphenylcyclopropenium ion **174** was found to be shielded by

(**173**)



(**174**)

(**175**)

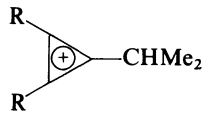


(**176**)

38.8 ppm with respect to **173**[186]; this indicates that phenyl plays a significant role in charge delocalization.

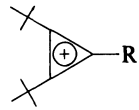
The chemical shifts of the ring carbons of **173** and **174** fit quite well into a correlation with π-electron density. This correlation has as its limiting members **175** and **176** whose ring carbon chemical shifts range over more than 120 ppm with the corresponding π-electron density values varying between ca. 0.5 and 1.20[185].

Stang and Mangum[187] reported that ^{1}H-NMR parameters of **177** were δ 1.45 (d, J = 7 Hz, 6H); 2.81 (s, 6H); 3.42 (sept., J = 7 Hz, 1H); the methyl and methine protons are significantly deshielded, as are the methylene protons of **178**.



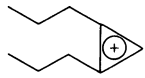
(**177**, R = Me)
(**178**, R = Et)

Under similar conditions Ciabattoni and Nathan found markedly low field absorptions for the methyl and methylene protons on the carbon atom directly bonded to the three-membered ring of a number of di-*t*-butylalkyl (aryl) cyclopropenium ions[178]. Thus for **179** and **180** δ H_a is 2.98 and 3.33 ppm respectively; for **181** δ H_a = 1.58 ppm which is appreciably downfield from the protons of di-*t*-butylcyclopropenone, 1.34 ppm.



(**179**, R = $C(H_a)_3$)
(**180**, R = $C(H_a)_2CH_2CH_2CH_3$)
(**181**, R = $C[C(H_a)_3]_3$)

Earlier, Breslow's group found that in 50% aq. H_2SO_4 (and relative to external C_6H_6) the ^{1}H-NMR spectrum of **182** showed a sharp band at 4.15 ppm together with *inter alia* a triplet at 3.12 (upfield) for the methylene protons adjacent to the ring[188].



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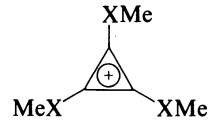
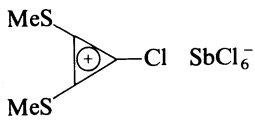


(183, X = S ; δ2.85)
(184, X = Se; δ2.72)
(185, X = Te; δ2.38)

In $CDCl_3$ the chemical shift of the methyl groups in **183–185** is shifted to higher field as the electronegativity of X decreases. The spectrum of **186** in CD_3CN showed separate closely spaced singlets at δ 2.92 and 3.07; this was interpreted as a rigid *exo/endo* alignment of the –SMe groups at room temperature brought about by hindered rotation[189].

Data from a number of diversely substituted cyclopropenium rings have been reported. In **187** the ^{13}C spectrum showed absorptions for C(1), C(2) at 133.7 ppm and C(3) at 99.0 ppm and in **188** the observed chemical shifts were C(1), C(2) 131.5, C(3) 113.5 ppm[190].



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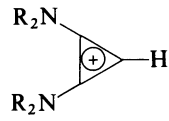
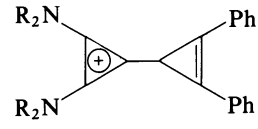


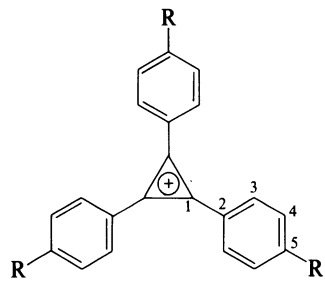
(187, R = *i*-Pr)



(188, R = *i*-Pr)

The ^{13}C chemical shifts of **174** and **189a** are shown in Table 14[191].

The calculated charge densities at C(1) in **174** are +0.330 and at C(1) in **189a** +0.219; this suggests that ca. 35% of the charge at this position is lost in going from **174** to **189a**. In the analogous triphenylmethyl carbocations the loss is appreciably greater. Therefore in the cyclopropenium ion **189a** (compared to the corresponding Ar_3C^+) there is a decreased contribution from the immonium resonance form[192]. The same group subsequently examined *inter alia* the ion **189b** and concluded that ca. 7% of the charge estimated to be originally present on the cyclopropenium ring in **174** is withdrawn in **189b**[192].



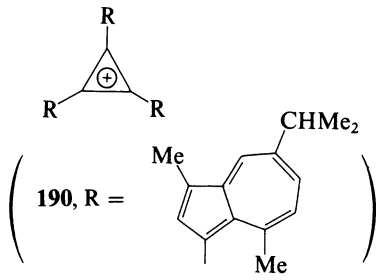
(189a, R = N(Pr-*i*)$_2$)
(189b, R = ◁)

TABLE 14. ^{13}C chemical shifts of **174** (in $ClSO_3H$) and **189a** (in $CDCl_3$)[a]

	C(1)	C(2)	C(3)	C(4)	C(5)
174	136.0	115.2	134.1	127.2	133.6
189a	155.4	120.1	135.9	131.2	139.2

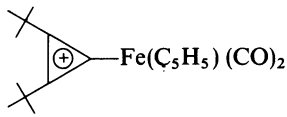
[a] Numbering as in **189**.

Comparison of the ^1H-NMR spectrum of **190** with that of guaiazulene itself and consideration of the derived chemical shift increments indicated partial delocalization of



190, R =

positive charge from the three- to the seven-membered ring, resulting in a reasonable contribution from a tropylium-like structures[193]. The same authors also reported the ^{13}C chemical shifts of triferrocenyl cyclopropenium cations[194, 195] in which the delocalization of the positive charge to the remote five-membered ring is mediated by the metal. The σ-dicarbonyl-cyclopentadienyliron derivatives of cyclopropenium salts, exemplified by **191**, have been synthesized by Gompper and Bartmann[196], and showed two singlets at 1.49 ppm and 5.41 ppm in the expected ratios in the ^1H-NMR spectrum.



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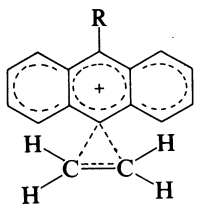
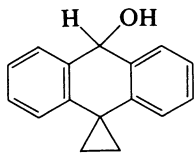
Two topics with a different emphasis, though not cyclopropenium ions, are noteworthy. Thus Winstein proposed structures **192** and **193** for the structures of the ions generated



(192, R = H)
(193, R = OH)



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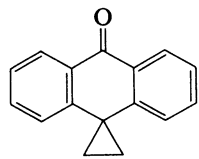


(195)

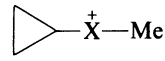
from precursors **194** and **195** respectively[197]

Olah and coworkers studied the halonium ions **196–198** for which the ^{13}C-NMR parameters are shown in Table 15[198]. The marked increase in shielding observed between

TABLE 15. ^{13}C-NMR spectral data of halonium ions **196–198**

	δC_α	$^1J_{C_\alpha H}$	δC_β
196	53.80	214.9	9.40
197	46.10	215.0	9.40
198	13.10	196.5	9.30

the chloronium and iodonium ions was stated to be consistent with the inductive effect of the halogen atoms; however, another effect merits consideration, viz. the well documented but ill-understood 'heavy atom effect' which causes significantly enhanced shielding of carbons bonded to iodine[199].



(**196**, X = Cl)
(**197**, X = Br)
(**198**, X = I)

X. FLUORINE AND FLUORINE-CONTAINING GROUPS BONDED TO CYCLOPROPANE AND CYCLOPROPENE RINGS

The ^{1}H-NMR spectrum of fluorocyclopropane (**199**) with that for cyclopropane (**1**)[79] for comparison is given in Table 16[4, 12]. The vicinal coupling constants in Table 16 are

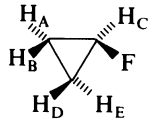
TABLE 16. ^{1}H-NMR chemical shifts of **199**[a] and **1**

	H_A	H_B	H_C	$J_{H_AH_B}$	$J_{H_AH_C}$	$J_{H_BH_C}$
199[a]	0.69	0.27	4.32	−6.69	5.89	2.39
Cyclopropane	0.20	0.20	0.20	−4.34	8.97	5.58

[a] 8 mol % **199** in 38 mol % C_6H_6.

depressed by the strongly electronegative substituent[200]; indeed a plot of the sum of the vicinal coupling constants for 1-substituted acenaphthenes (**200**), as models, gave a reasonable correlation with those of cyclopropanes. The fluoro derivatives have the smallest values in both cases[201]. The observed proton–proton coupling constants for **199** that were not cited in Table 16 were $J_{H_BH_E} = J_{H_AH_D} = 7.70$ Hz, $J_{H_AH_E} = 10.80$ Hz and $J_{H_BH_D} = 12.01$ Hz. Fair agreement with these values was found by means of SCF finite perturbation theory[200].

The geminal proton–fluorine coupling constant $^2J_{HF} = 64.90$ Hz in fluorocyclopropane was determined by Scherr and Oliver[12]; the *trans* $^3J_{H_AF} = 9.87$ Hz and its *cis* counterpart $^3J_{H_BF} = 21.02$ Hz were found to have the same relative sign. Other examples of $^2J_{HF}$ values were provided by the work of Ando and coworkers[202].



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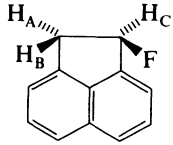
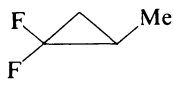
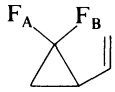


(200)

Few data are available for geminal difluorocyclopropanes. In **201** the geminal coupling $^2J_{FF} = 157$ Hz was determined[202,203]. More recently, Dolbier's group observed that the



(201)



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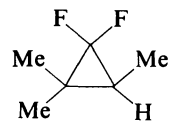
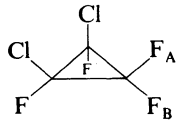


(203)

^{19}F-NMR spectrum of **202** contains an AB quartet with a chemical shift, $\phi = 135.0$ ppm (from $CFCl_3$) at the midpoint; the geminal coupling $^2J_{FF} = 156.5$ Hz with $\Delta\nu = 1235.6$ Hz were reported[204]. Also apparent were vicinal couplings, *cis* $^3J_{HF} = 12.5$ Hz and *trans* $J_{HF} = 4$ Hz. In **203** the probable $^2J_{FF}$ equals 153.6 Hz[204,205].



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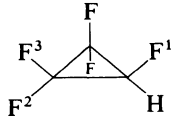
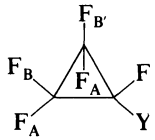


(205)

From study of a number of fluorinated cyclopropanes, Sargent found that the geminal coupling $^2J_{FF}$ lay in the range 170–210 Hz in accord with cited precedent; in the particular cases of **204** and **205** the values of $^2J_{FF}$ were respectively 174 and 208 Hz[206]. Sargent then suggested that for diagnostic work ring-opened products could be characterised *inter alia* by their large geminal FF coupling constants[207]. In the case of **205** the ^{19}F chemical shifts ($CFCl_3$) are F^1, 241.9; F^2, 151.6; F^3, 161.5 ppm.

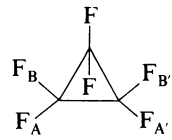


(**206**, Y = Cl)
(**207**, Y = Br)
(**208**, Y = I)

From the data in Table 17 it is readily seen that for the halogenopentafluorocyclopropanes **206–208** the geminal $^2J_{FF}$ values are in the range 180–190 Hz and positive in sign[208].

TABLE 17. Coupling constants for halogenopentafluorocyclopropanes

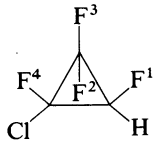
Substituent	J_{AB}	$J_{AB'}$	$J_{AA'}$	J_{BB}	J_{AX}	J_{BX}
Cl	189.04	0.88	4.87	10.73	− 5.82	8.27
Br	185.72	2.42	1.91	10.41	− 10.13	6.59
I	181.44	4.34	− 1.29	9.78	− 15.44	4.72



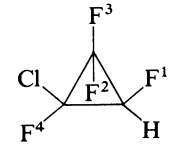
(209)

The ^{19}F spectrum of hexafluorocyclopropane **209**, dissolved in *p*-ethoxybenzylidene-*p*-*n*-butylaniline, yielded the coupling constants $J_{F_AF_B} = 204.4 \pm 1.3$; $J_{F_AF_{B'}} = 11.1 \pm 0.4$ and $J_{F_AF_{A'}} = -1.3 \pm 0.3$ Hz[209]. It might be noted that the value of $J_{F_AF_{B'}}$ in **209** is out of line with those cited in Table 16, and indeed shortly thereafter the assignments of the vicinal coupling constants in **209** were reversed[210].

Sargent[207] noted that for vicinal coupling constants, *cis* J_{HF} and *cis* J_{FF} are in general larger than the corresponding *trans* J_{HF} or J_{FF}. In the case of proton–fluorine couplings, the figures from a number of cyclopropanes revealed that values of *cis* $^3J_{HF}$ ranged from



(210)

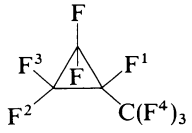


(211)

$^3J_{HF^2} = 9.1$ Hz in **211** to $^3J_{HF^4} = 16.8$ Hz in the same compound. The *trans* vicinal couplings were shown to have magnitudes between $^3J_{HF^3} = 1.3$ Hz in **205** and **210** to $^3J_{HF^3} = 2.1$ Hz in **211**.

The situation is less clear cut in the case of *cis*- and *trans*- vicinal fluorine–fluorine coupling in that the range of couplings overlaps, although with one exception *cis* J_{FF} is greater than *trans* J_{FF}. This is exemplified in the case of **205** in which *cis* $J_{FF} = 9.8$ Hz compared to *trans* $J_{FF} = 4.9$ Hz. The exception is **211** in which *trans* $J_{F^1F^4} = 11.1$ Hz and the *trans* coupling $^3J_{F^1F^2} = 2.8$ Hz, with the *cis* coupling of intermediate value $^3J_{F^2F^4} = 5.7$ Hz. The magnitude of these couplings is of course a function of the substituent pattern and the precise role of substituents does not appear to have been delineated completely.

Fluorine–fluorine coupling through four bonds was noted in **212**, thus the *cis* coupling $^4J_{F^2F^4} = 7.7$ Hz and this too was found to be rather greater than its *trans* counterpart, $^4J_{F^3F^4} = 6.0$ Hz. Thus from the limited available data the coupling with the potential for the contentious 'through space' mechanism gives a larger value than the *trans* coupling in which the relevant fluorines are able to adopt the W conformation that is frequently adopted (or enforced) when sizeable *trans* ^4J values are observed. In **213** Sargent[207] also



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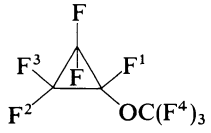
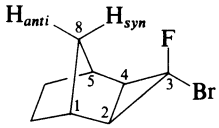


(213)

noted a coupling $^5J_{F^2F^4} = 4.6$ Hz, and in this instance also the *cis* coupling with the potential for close approach of the relevant fluorines has a larger magnitude than its *trans* counterpart $^5J_{F^3F^4} = 1.2$ Hz.

An interesting case of long-range couplings of the proton–fluorine type was provided by the ^{19}F-NMR spectrum of **214**[211] which gave a quintet 146 ppm upfield from CCl_3F; this absorption showed $^3J_{FH_2} = 3.5$ Hz (rather low when compared with $^3J_{FH_B} = 6.3$ Hz,



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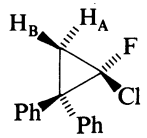
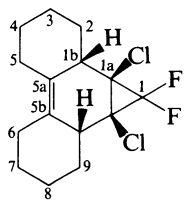


(215)

cited for **215**), $^3J_{HF}$ being 'notoriously sensitive to substituents'[212]. There are long-range couplings between F and both the C(8) protons; these have values $^5J_{FH_{8anti}} = 3.0$ Hz and $^5J_{FH_{8syn}} = 3.6$ Hz. The *syn* coupling is the larger and has the possibility of a through space mechanism, more particularly since H_{syn} and F are closer than the sum of their van der Waals' radii. This will of course induce non-bonded repulsions which the authors consider may result in the separation of C(3) and C(8); if this does occur it does so in such a way as to preserve Cs symmetry as indicated by the NMR spectrum.

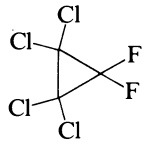
In a thorough investigation of the rigid compound **216** Halton and Officer[213] found that several of the carbons were coupled to fluorine. The values found were: for C(1), $^1J_{CF} = 312$, 292 Hz; for C(1a), $^2J_{CF} = 11.5$, 8.4 Hz; for C(1b), $^3J_{CF} = 2.7$, 1.9 Hz. Two longer



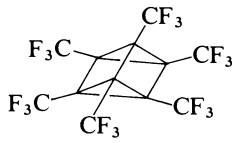
(216)

range coupling constants in which only one fluorine participated were: for C(5a), C(5b), $^4J_{CF} = 3.5$ Hz and for C(5), C(6), $^5J_{CF} = 2.5$ Hz. The stereochemistry assigned, viz. cyclopropane ring *endo*, results in one of the fluorine atoms being in close proximity to C(5).

A further characteristic feature of the spectrum of **216** is the coupling constant $^1J_{CF}$, not hitherto mentioned in this section. Other comparable values were reported *inter alia* by



(217)

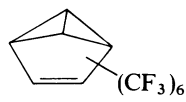


(218)

Tobey and West[214] who observed $^1J_{CF} = 313$ Hz in **217** and Roberts' group[1] who found $^1J_{CF} = 328.7$ Hz for hexafluorocyclopropane.

Further data on fluorine couplings are included in Refs 215a and especially 215b.

Trifluoromethyl groups bonded to cyclopropane rings have received a limited amount of attention, mainly on account of synthetic problems associated with the substituent. The prismane **218** was synthesized by two groups and a singlet at δ 12.7 (with respect to external CF_3CO_2H in n-C_5F_{12}) was observed. A three band system of equal intensity at 20.3, 17.55 and 13.9 ppm was noted by Barlow and coworkers for **219**[216].



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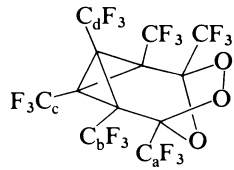
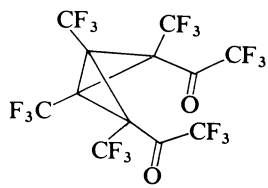


(220)

Kobayashi and coworkers reported on the ^{19}F chemical shifts of the bicyclo[1.1.0]butane derivative **220**[217]. The chemical shifts ($PhCF_3$ as a standard) were for the itemized carbons, $C_a - 10.6$, $C_b + 2.0$, $C_c + 11.0$, $C_d + 11$ ppm.



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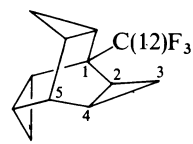


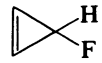
(222)

Three absorptions were obtained in the ^{19}F-NMR spectrum of **221**; that for the $COCF_3$ group was assigned to the signal at -13.6 ppm. The other two absorptions at 11.2 and 2.4 ppm were unassigned[218].

The ^{13}C–^{19}F coupling constants of the bridgehead substituted compound **222** showed that whereas the cyclopropyl carbons C(3) and C(4) remote from fluorine appeared as singlets in the proton decoupled spectrum, C(2) (δ 9.75) showed $^3J_{CF} = 2.8$ Hz[219]. The corresponding constants for C(1) and C(12) were 27.3 and 279 Hz.

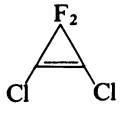
The ^1H spectrum for 3-fluorocyclopropene, **223**, showed an absorption for the vinyl proton at δ 7.7, $J_{HF} = 3.2$ Hz, $J_{HH} = 1.5$ Hz and the tertiary proton δ 5.0, $^2J_{HF} = 110$ Hz.

A doublet of triplets for the ^{19}F absorption appeared at -145 ppm. The atypically large geminal coupling constant $^{2}J_{HF}$ was noted; more usually the coupling constant is ca. 60 Hz and the large value was taken to indicate a large angle CFH[220].



(223)

The ^{19}F shifts, upfield from $CFCl_3$, of a number of disubstituted 3,3-diffuorocyclopropenes have been reported[221,222]. In the examples shown the chemical shifts in δ are: **224**, -99.8; **225**, -98.1; **226**, $F_a = -96.7$, $F_b - 145.1$. For **224** and **225** $^{1}J_{CF}$ were 292 and



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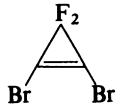

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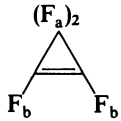
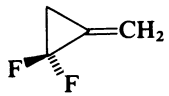


(226)

320.5 Hz respectively. In the tetrafluoro compound $^{1}J_{CF_a} = 292.9$ Hz and for the vinyl fluorine a characteristically larger value $^{1}J_{CF_b} = 444.5$ Hz was found.

The conversion of **227** to **228** followed by Dolbier's group[223] indicated a preference of fluorine for the exocyclic positions. The ^{19}F absorption of the starting material (in $CDCl_3$



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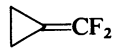
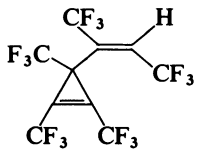


(228)

and relative to TFA) occurred at δ 53.0 whereas those of the vinyl fluorines of **228** were a pentuplet, δ 9.13, $J = 4$ Hz.

A small number of trifluoromethyl-substituted cyclopropenes has been made. Laganis



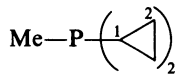
(229)

and Lemal[224] reported absorptions at δ 60.23 (6F), 63.14 (3F); 67.78 (3F) and 68.08 (3F) for the CF_3 groups of **229** though without specific attribution.

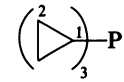
XI. PHOSPHORUS AND LESS COMMON NUCLEI BONDED TO A CYCLOPROPANE RING

A small number of publications have been concerned with phosphorus–cyclopropane derivatives. The state of oxidation of the phosphorus is important, as is the valency and it is as yet difficult to form an overall picture.

Schmidbaur and Schier[225] found that for the cyclopropane carbons of **230** δ C(1) = 8.93, $^1J_{PC}$ = 4.9 Hz; δ C(2) = 2.9, $^2J_{PC}$ = 11.7 Hz and 3.9, $^2J_{PC}$ = 10.7 Hz. The non-



(230)

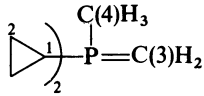


(231)

equivalence stems from the prochirality with respect to the configurationally fixed phosphorus atom. The methyl carbon absorbs at δ 12.05, $^1J_{PC}$ = 12.7 Hz, and the ^{31}P absorption occurs at − 8.37 ppm (relative to H_3PO_4). In the case of **231** δC(1) = 7.28, $^1J_{PC}$ = 3.9 Hz and δC(2) = 3.22, $^2J_{PC}$ = 10.7 Hz. With respect to **230** the ^{31}P absorption is significantly deshielded at 16.34 ppm.

In the same investigation[225] the spectral parameters of the ylides **232** and **233** were reported; the spectral parameters though not completely understood are characteristic and diagnostic.

The methyl protons of **232** are coupled to phosphorus $^2J_{PH}$ = 13 Hz and the ylide methylene protons (δ − 1.13 in C_6D_6) show $^2J_{PH}$ = 9 Hz. The ^{13}C-NMR spectrum of **232**



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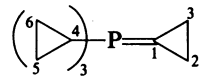

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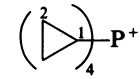


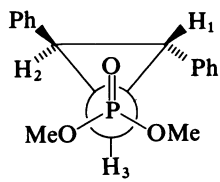
(234)

shows δC(4) = 17.0, $^1J_{PC}$ = 71.3 Hz; δC(1) = 7.5, $^1J_{PC}$ = 81.1 Hz; δC(2) = 0.65, $^2J_{PC}$ = 2.0 Hz; δC(3) = − 22.16, $^1J_{PC}$ = 113.2 Hz. The ^{31}P absorption of **232** occurs at δ 23.53.

The carbon absorptions of **233** again show a high field ylide carbon δC(1) = − 19.44, $^1J_{PC}$ = − 18.3 Hz and other cyclopropyl absorptions at δC(2), 5.31, $^2J_{PC}$ = 10.9 Hz; δC(4), 3.98, $^1J_{PC}$ = 83.0 Hz; δC(5), − 1.93, $^2J_{PC}$ = 4.3 Hz. The ^{31}P chemical shift of **233** occurs at 20.86 ppm.

In trifluoroacetic acid the protons of **234** absorb in the range 0.33–1.00 ppm. The ^{13}C parameters are characteristically different, δC(1) = 0.56, $^1J_{PC}$ = 89.8 Hz; C(2) = 5.78 (br singlet). The quaternary carbon now absorbs at δ44.05.

Regitz' group[226] found that the vicinal coupling constants in **235** were, *cis* $^3J_{PH_1}$ = 16.9 Hz and *trans* $^3J_{PH_2}$ = 13.9 Hz. These are in accord with general experience of



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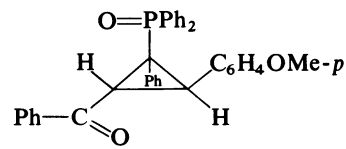
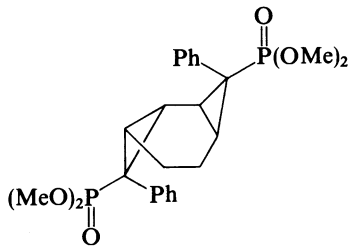


(236)

vicinal coupling constants in cyclopropanes. For **235** the *trans* coupling constant $^3J_{H_1H_3}$ = 6.4 Hz and the *cis* counterpart $^3J_{H_1H_2}$ = 9.4 Hz.

The same group[226] also reported partially on the coupling constants of **236**; here the *trans* $^3J_{HH}$ = 7 Hz and both ^{1}H absorptions were split by phosphorus to the extent of 14 and 12 Hz probably corresponding to *cis* and *trans* couplings, although specific attribution was not attempted.

From the non-first order (ABCX) spin system in **235** Scherer and coworkers[227] extracted all the coupling constants relating protons and phosphorus. The analysis yielded $J_{H^1H^2}$ = 6.36 Hz; $J_{H^1H^3}$ = 6.40 Hz, $J_{H^2H^3}$ = 9.81 Hz, J_{H^1P} = 17.01 Hz; J_{H^3P} = 1.58 Hz; J_{H^3P} = 13.87 Hz. The authors comment that it is always found that *cis* $^3J_{PH}$ = 10 × (*trans* $^3J_{PH}$) and they extrapolate to compounds **237** and **238** which are considered to have the *exo* configuration since $^3J_{HP}$ = 16–17 Hz. Further similar data are reported by Maas and Regitz[228].



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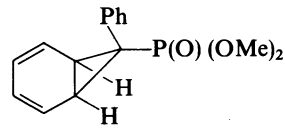
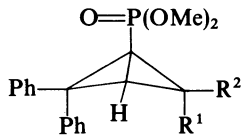


(238)

The bicyclo[1.1.0]butane derivatives **239** and **240** exhibited the expected large *cis* coupling constant between the bridgehead substituents[229]. For **239** and **240** the respective values of $^3J_{HP}$ are 23.5 and 24 Hz. The corresponding absorptions of the bridgehead proton are 3.65 and 3.30 ppm.

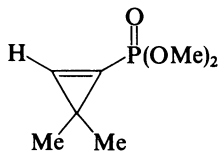


(239, $R^1 = R^2$ = Ph)
(240, $R^1 = R^2$ = Me)
(241, R^1 = Me, R^2 = *t*-Bu)

In **240** the methyl *trans* to phosphorus showed δ 0.60, $^4J_{PH}$ = 1.5 Hz and its *cis* counterpart δ1.38 appeared as a singlet with $^3J_{PH}$ = 25.0 Hz[230]. The *t*-butyl derivative **241** contained an absorption at δ 0.63, $^4J_{PH}$ = 2.0 Hz, together with a singlet δ 1.15 for the *t*-butyl protons which do not couple to phosphorus.

Regitz' group also showed that in **242** the olefinic proton absorbs at δ 8.38 with a vicinal coupling to phosphorus $^3J_{PH}$ = 3.0 Hz[231]. The ring methyl groups are also coupled to phosphorus with parameters δ 1.30, $^4J_{PH}$ = 3.0 Hz; δ 1.71, $^4J_{PH}$ = 3.0 Hz. In **243** all protons were coupled to phosphorus $^4J_{PH_a}$ = 1 Hz; $^3J_{PH_b}$ = 3 Hz ($^3J_{HH}$ = 4.5 Hz); $^4J_{PH_c}$ = 3 Hz[230].

The ^{1}H chemical shifts and inter-proton coupling constants of cyclopropyl lithium (**244**) were determined by three groups[12,74,232]. This compound, apart from its intrinsic interest,



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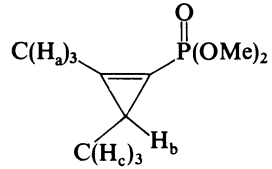

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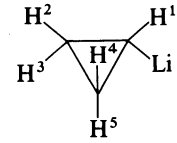
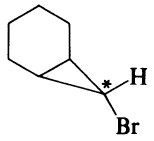


(244)

is of relevance in that the substituent represents the lower end of an electronegativity scale. Accordingly cyclopropyl lithium has the most positive $J_{H^1H^2} = 11.31$ Hz, $J_{H^1H^3} = 9.12$ Hz and the least negative $J_{H^2H^3} = -1.58$ Hz together with the smallest positive values of $J_{H^2H^4} = 7.71$ Hz, $J_{H^2H^5} = 3.17$ and $J_{H^3H^5} = 6.42$ Hz. Coupling constants of *inter alia* cyclopropyl lithium have been treated theoretically[200].

A cyclopropane ring fused to a further ring as in **245** has proved to be a particularly apposite substrate for the detection of the so-called halolithiocarbenoids such as **246** (this compound is formed from the geminal dibromide with *n*-butyl lithium)[233]. At -100°C in



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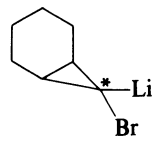

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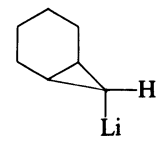
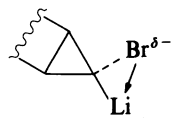


(247)

tetrahydrofuran C_4H_8O/C_4D_8O (9 : 1) the ^{13}C chemical shift of the ^{13}C-enriched carbon (shown as*) in **245** was 24.5 ppm compared with a downfield shift of 62.5 ppm to δ 87.0 for **246**. This very large downfield shift, which is reproduced in other examples cited, bears a marked contrast to the much smaller downfield shift, from 9.6 ppm to 10.0 ppm, experienced by this carbon on the corresponding introduction of a lithium into **99** to give **247**. The large downfield shift encountered in forming **246** is interpreted in terms of either a weakening of the C–Br bond as in **248** or possibly even rehybridization as depicted in **249**. A full paper describes extensions to non-cyclopropanoid systems[234].



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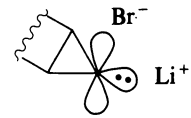
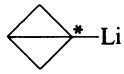


(249)

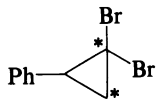
The same group also reported several related compounds involving ^{13}C and ^{6}Li labelling[235]. In the case of ^{13}C-enriched **246** the ^{13}C absorption was a triplet with $^1J_{CLi} = 17.0$ Hz; the spectra were registered at temperatures down to -150°C and the coupling disappeared reversibly above -70° C consistent with a change of bonding associated with aggregation.

The ^{13}C shift of the bridgehead carbon in bicyclo[1.1.0] butane changes from -4.0 ppm to -14.7 in **250**, with $^1J_{CLi} = 10.3$ Hz (quintet). Signal multiplicity is a function of substrate aggregation which is not germane to this review.

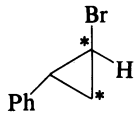


(250)

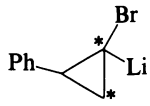
With the aid of phenylcyclopropanes the ^{13}C, ^{13}C coupling constants between the starred (^{13}C-enriched) carbons in **251–254** were determined. The results show that introduction of a lithium atom brings about a significant decrease in the values of J. This is attributed to a strong Fermi contact interaction between carbon and lithium.



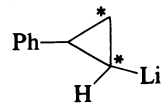
(**251**, $^1J_{cc}$ = 13 Hz,)



(**252**)



(**253**)

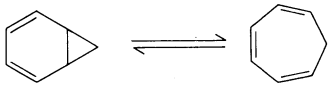


(**254**)

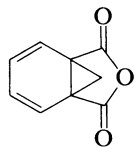
Chemical shifts and coupling constants have been determined in for example cyclopropyl magnesium bromide and the compounds formed with gallium, silicon, mercury, tin and lead[12]. A complete analysis of the metal satellite spectra of tetracyclopropyl lead and tin and dicyclopropyl mercury has been presented[236].

XII. NORCARADIENES

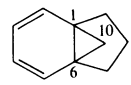
Norcaradiene (**255**) and cycloheptatriene (**256**) are related as valence tautomers and equilibrium is weighted heavily in favour of the monocyclic component; recently, **255** has



(**255**) (**256**)



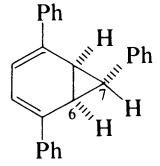
(**257**)



(**258**)

been detected spectroscopically (though not by NMR). At −170°C the estimate of $t_{1/2}$ = 63 s has been made for **255** and this renders the determination of the NMR spectrum difficult[237].

Eschenmoser[238] and Vogel[239] and their coworkers used locked tricyclic molecules for the isolation of norcaradienes. For **257** the cyclopropyl protons at 0.81 and 2.43 ppm showed $^2J_{HH}$ = 4.5 Hz[238], and for **258** the C(10) protons absorbed at −0.4 and 1.43 ppm with the $^2J_{HH}$ − 4 Hz. The first example of a simple norcaradiene containing a hydrogen at C(7) was **259** which in the ^{1}H-NMR spectrum showed absorptions at 1.98 ppm (H_7, J = 5.2 Hz) and 3.88 ppm (H_1, H_6, J = 5.52 Hz); thermolysis of this compound at ca.120° C established equilibrium with the cycloheptatriene[66]. Slightly earlier, 7,7-dicyanonorcaradiene (**260**), δ H_1H_6 = 3.47, had been synthesized and the rather low field absorptions for the bridgehead protons was attributed to the combined deshielding effects of two double bonds and two cyano groups[240]. The ^{1}H-NMR spectrum of **260** has been completely analysed[241].



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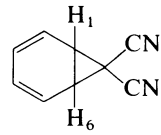
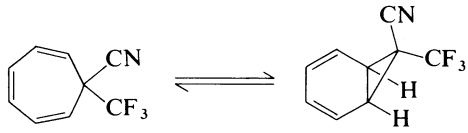


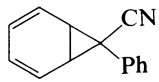
(260)

It was shown also that whereas the 7-cyano-7-trifluoromethyl derivative consisted of an equilibrium between norcaradiene and cycloheptatriene, in the case of 7-cyanocycloheptatriene none of the bicyclic tautomer could be detected.

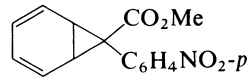


(261) (262)

A rapidly equilibrating mixture of **261** and **262** was indicated by both ^{1}H and ^{19}F variable temperature studies[242]. The absence of a third signal in the low temperature ^{19}F spectrum suggested that only one of the two possible isomers of **262** is present. Integration of the ^{1}H-NMR spectrum at $-112°$ C gave a ratio **261** : **262** of 3.45; the ^{19}F spectrum gave a similar result[242]. The low temperature ^{1}H absorptions of H_1,H_6 in **261** and **262** are at δ 5.40 and 2.95 respectively. The doublet in the room temperature spectrum at 4.70 is intermediate in chemical shift between a norcaradiene and a cycloheptatriene and the single norcaradiene isomer is taken to be that depicted in **262** with the less bulky cyano group in the *endo* position. A similar situation prevailed for **263**[243]. For the conversion of

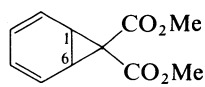


(263)



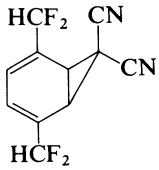
(264)

264 to the cycloheptatriene the parameters $\Delta H = 3.5 \pm 0.2$ kcal mol^{-1} and $\Delta S = 11.0 \pm 0.8$ cal deg^{-1}mol^{-1} were found; kindred systems were also investigated[244]. In addition to these ground state values Görlitz and Günther deduced that the conversion of **265** to the cycloheptatriene was associated with a value $E_a = 7$ kcal mol^{-1}; at low temperatures ($-139°$ C) in an unusual solvent mixture CCl_2F_2 : Me_2CO : $CHCl_3$ (5 : 3 : 2) the H_1 absorption occurred at 2.86 ppm.

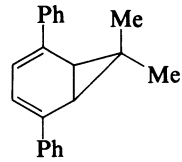


(265)

In a quest for the reasons favouring the norcaradiene tautomer it was noted that the norcaradiene form was favoured by strongly electron-withdrawing substituents or by incorporation into external π systems with the correct geometric and symmetry disposition for interaction[245]. Also Roberts and coworkers referred to the 'remarkable but not wholly clarified ability' of two 7-cyano groups to stabilize norcaradiene[246] and provided a further example of a preferred norcaradiene in **266**. The variable temperature ^{19}F-NMR spectrum of **266** indicated magnetic non-equivalence of the geminal fluorines during inversion of the



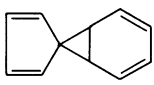
(266)



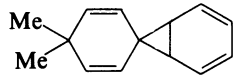
(267)

three-membered ring via cycloheptatrienes. Paquette and Leichter also noted that in **267** the norcaradiene was clearly the preferred tautomer[245].

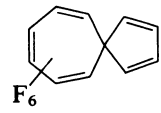
Attempts were made to influence the position of the equilibrium by incorporation of C(7) in a notional norcaradiene into a spiro system. The presence *inter alia* of a multiplet at 3.60 ppm requires the norcaradiene **268**[247]; a symmetrical multiplet at 3.53 ppm supports the norcaradiene structure, **269**[248]. By way of contrast the hexafluoro compound **270**



(268)

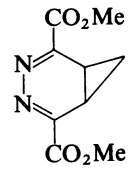


(269)



(270)

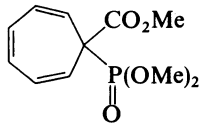
possesses the structure shown[249]; in common with fluorobullvalene (see below) fluorine shuns the cyclopropyl position. A norcaradiene-type structure was found for the heteroatom analogue **271** and the inversion itinerary was considered[250].



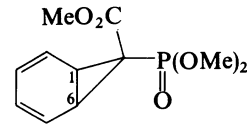
(271)

Maas and Regitz' collated much earlier data and studied the influence of phosphonate esters at C(7). For the equilibrium **272**⇌**273** values of $\Delta H^\circ = -872 \pm 49$ cal mol^{-1} and $\Delta S^\circ = -0.49 \pm 0.19$ cal deg^{-1}mol^{-1} were determined with the cycloheptatriene being more stable. In **273**, δ H$_1$,H$_6$ = 4.93 with $^3J_{PH}$ = 14.5 Hz, a value which is indicative of a *cis* coupling and which supports the *exo* configuration of the phosphoroester group. Replacement of CO_2Me groups of **265** by $PO(OMe)_2$ groups (yielding **273**) results in a

destabilization of the bicyclic moiety by $\Delta\Delta H^\circ = 1$ kcal mol^{-1} with respect to the cycloheptatriene.

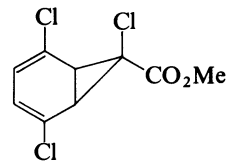


(272)



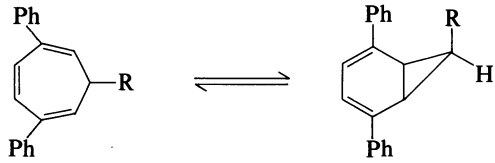
(273)

Additionally it was found that the presence of two chloro groups at C(2) and C(5) with a CO_2Me group at C(7) as in **274** results in the norcaradiene being more stable by 3 kcal mol^{-1}.



(274)

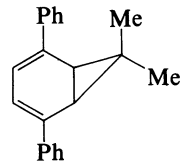
Staley and coworkers[251] noted that the equilibrium for **275**⇌**276** is characterizd by $K < 0.1$ at 25° C. However for the corresponding equilibrium **277**⇌**278**, $K = 0.7$, signifying 41 % norcaradiene, and for **279**⇌**280**, $K \approx 0.3$ (24 % of **280**). Introduction of a piperidino group at C(7) to give **277**⇌**278** brings about a relative stabilization of the norcaradiene



(**275**, R = H)
(**277**, R = 1-piperidino)
(**279**, R = cyclohexyl)

(**276**, R = H)
(**278**, R = 1-piperidino)
(**280**, R = cyclohexyl)

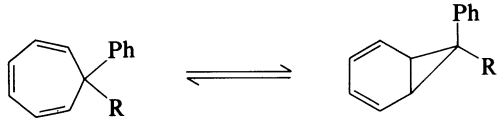
form by > 1 kcal mol^{-1}. It was also found that although there is very little norcaradiene (**276**) at equilibrium the introduction of methyl groups to give **281** ($\delta H_1, H_6 = 2.38$) results almost exclusively in the norcaradiene form.



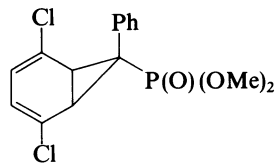
(281)

^{13}C-NMR spectroscopy has also been employed to address the question of the norcaradiene/cycloheptatriene equilibrium. Thus whereas in cycloheptatriene the ^{13}C chemical shifts C(1), C(6) = 123.3, C(7) = 28.8 ppm were reported, for the locked norcaradiene **258**, C(1), C(6) absorbed at 38.6 ppm and C(10) at 20.2 ppm[252]. The observed ^{13}C chemical shifts of the 'cyclopropane' carbons at values appreciably shielded from those in definitive norcaradienes is a manifestation of a reversible equilibrium with rapid exchange leading to an averaged chemical shift.

This approach led to a value for $K = 0.42$ in the case of **282**⇌**283** (25° C, CCl_4), rising to 1.49 at −81° C. For the corresponding phosphonate ester **284** ⇌ **285** the value of $K = 3.78$ (25 °C rising to 9.95 at −99° C)[253]. In **286** a norcaradiene structure was indicated by both



(**282**, R = CO_2Me) (**283**, R = CO_2Me)
(**284**, R = P(O)$(OEt)_2$) (**285**, R = P(O)$(OEt)_2$)

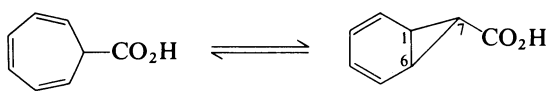


(**286**)

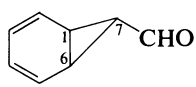
the H_1, H_6 and C(1), C(6) chemical shifts together with the coupling constant $J_{H_1H_6}$ = 9.05 Hz; the further coupling constant $^3J_{HP}$ = 16.2 Hz indicates a *cis* relationship between these atoms, requiring phenyl to be *endo*.

The Büchner acids exemplified by **287** were originally formulated as norcaradienes. However, Doering's group, in work which probably kindled modern interest in this subject despite an 'enigmatic' numbering system[254], demonstrated that these compounds were cycloheptatrienes. Subsequently line broadening at low temperatures has been shown to occur for only C(1), C(6) and C(7) in the ^{13}C-NMR spectrum[255].

An investigation by Wehner and Günther of the low temperature ^{1}H-NMR spectrum of **287** indicated a new signal of low intensity at δ 0.52 at temperatures below −110° C,



(**287**) (**288**)



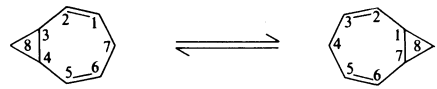
(**289**)

attributable to H_7 in **288**[255]. At $-150°$ C the H_7 absorption showed $W_{1/2} = 10$ Hz in accord with a *trans* relationship with H_1, H_6. At low temperature a value of $\Delta G°$ ($-150°$ C) $= 0.91$ kcal mol^{-1}.

Günther's group detected a small proportion of 7-norcaradienecarboxaldehyde[256] (**289**) in the room temperature 400 MHz ^{1}H-NMR spectrum. Low temperature studies suggested a conformational equilibration of two cycloheptatrienes in addition to the valence tautomerization. At $-145°$C, the value of $\Delta G° = 0.55$ kcal mol^{-1}. The *exo* configuration of the less abundant tautomer **289** is thought to be alone in permitting the bisected geometry of the aldehyde which enables an optimum electronic interaction with the cyclopropane ring to take place.

XIII. HOMOTROPILIDENE, BULLVALENE AND DERIVATIVES

Bicyclo[5.1.0]octa-2,5-diene (homotropilidene), **290**, undergoes a degenerate Cope rearrangement to **290a**. At room temperature the ^{1}H-NMR spectrum of **290** consists of a

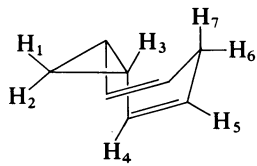


(290) **(290a)**

slightly broadened peak at 5.8 ppm together with a broad envelope centred at ca. 2 ppm and with a spread of approximately 3 ppm[257]. At $+180°$ C a sharply defined spectrum is observed and on cooling to $-50°$ C the spectrum is well resolved and endowed with fine structure. Spectra at the different temperature are shown[257].

The spectrum at $-50°$ C is in accord with a slow rate for the degenerate Cope rearrangement and in addition to four vinylic protons at δ5.7, two allylic protons at δ 2.8, there is also a single cyclopropyl proton, δ 0.3; two tertiary cyclopropyl protons absorb between δ 1–2 and a second cyclopropyl proton is thought to be deshielded by the double bonds.

The *trans*-like structure depicted in **291** is favoured over the range -50 to 180° C (from the ^{1}H-NMR spectrum); in the *cis* counterpart the protons H_2 and H_6 will interact adversely. Nevertheless, the Cope rearrangement probably occurs via the *cis* conformation; at a sufficiently rapid rate this rearrangement causes H_1 and H_7; H_2 and H_6; H_3 and H_5 to become equivalent. Accordingly, under conditions of rapid rearrangement the ^{1}H-NMR spectrum is described in terms of four absorptions. From the slow exchange

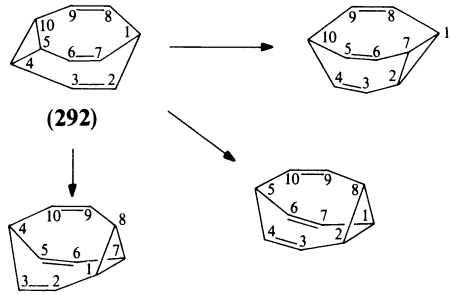


(291)

spectrum at $-58°$ C in CS_2, Günther's group subsequently showed that **290** exists as a flattened boat; coupling constants involving the cyclopropane ring are given[258].

Doering and Roth introduced conceptually a further *cis* double bond to replace the adversely interacting hydrogens H_2 and H_6[257]. The derived cage structure **292** now

enforces a *cis* conformation and degenerate Cope rearrangement is expected to be faster and if sufficiently rapid should result in a single sharp absorption in the ^{1}H-NMR spectrum; **292** was termed bullvalene (tricyclo[3.3.2.0^{4,6}]deca-2,7,9-triene). This brilliantly conceived molecule is one that every organic chemist active at the time[257] wishes he had devised first .



(292)

Bullvalene (**292**) has a threefold axis of symmetry and three reversible Cope rearrangements successively convert each cyclopropyl carbon C(10), C(5), C(4) into a bridgehead carbon; at the same time each carbon atom adjacent to the original bridgehead carbon C(1) become cyclopropyl carbons (i.e., C(2), C(7); C(2) C(8); C(7) C(8) respectively); see **292**. Thus a single Cope rearrangement can transform a cyclopropyl carbon of bullvalene into a bridgehead carbon, with the necessary consequence that a particular pair of carbon atoms adjacent to the bridgehead themselves become cyclopropyl carbons. By a progression of these rearrangements every one of the ten carbon atoms of bullvalene is converted into, for instance, a bridgehead carbon via the operation of a relatively small number of rearrangements. From the observation of a single NMR absorption in the ^{1}H-NMR spectrum, it follows that each of the 10!/3 (= 1 209 600) possible arrangements of carbon atoms are undergoing mutual interconversion.

Synthesis of bullvalene and examination of its ^{1}H-NMR characteristics was provided shortly thereafter by Merenyi and coworkers[259], who observed at 100° C a sharp signal at 4.22 ppm (line width 1.5 Hz). At −85° C two bands are centred on 5.65 ppm (unsymmetrical olefin absorption) and on 2.08 ppm (broad) (3 × cyclopropyl protons and a bridgehead proton). Rather surprisingly the triply allylic bridgehead proton absorbs with three cyclopropyl protons, a finding that is rationalized in terms of a 'ring current' of the cyclopropane ring that is located directly above the bridgehead pattern.

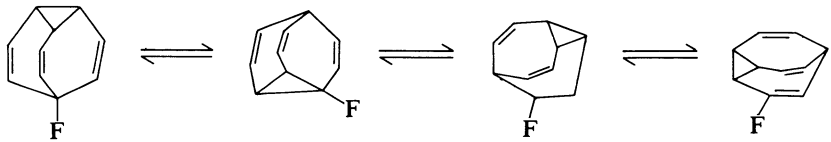
From the variable temperature ^{1}H-NMR spectrum Saunders found E_a = 11.8 kcal mol^{-1} and A = 12.3 s^{-1} for the degenerate rearrangement of bullvalene. The 'remarkably small probability and entropy barriers' to the rearrangements that involve both carbon–carbon bond breaking and making were ascribed both to extremely favourable geometry and to weakness of the bond[260]. These values were amended slightly to $E_a = 12.8 \pm 0.1$ kcal mol^{-1} with a frequency factor 0.8 × 10^{13} s^{-1}, and proton shifts also changed slightly[261]. In the solid state[262] the figures were again slightly different, E_a = 9.2 kcal mol^{-1}, frequency factor 0.2 × 10^{12} s^{-1}.

The proton decoupled ^{13}C-NMR spectrum of bullvalene at −53.2° C showed four singlets at 130.0, 129.3, 32.2 and 22.6 ppm[263]. On raising the temperature coalescence of the signals occurred to yield a broad singlet above 60° C and this became sharp at ~ 100° C. From line analysis of the ^{13}C-NMR data at thirty-five temperatures the following parameters for the rearrangement of bullvalene were reported: $E_a = 14.5 \pm 0.7$ kcal mol^{-1}; $\Delta G^{\ddagger} = 12.6 \pm 0.1$ kcal mol^{-1}; $\Delta H^{\ddagger} = 13.9 \pm 0.7$ kcal mol^{-1}; $\Delta S^{\ddagger} = 4.4 \pm 2.3$ e.u. at 25° C.

Very similar ^{13}C chemical shifts for bullvalene in the slow exchange limit were reported, and a set of activation parameters was calculated, though with omission of data around the coalescence temperature, at which point the lineshape is most sensitive to the dynamic process[264].

The 2D ^{13}C-NMR spectrum of bullvalene was considered by Huang and coworkers[265]. The deuterium NMR spectrum of partially deuterated bullvalene was studied over a temperature range -35 to $+115°$ C in liquid crystalline solvents[265]. The spectrum ranged from four distinct quadrupole doublets (relative intensities 3:3:3:1) on account of four non-equivalent groups of deuterium. After coalescence at ca. $-15°$ C one doublet is observed at high temperature. Similar activation parameters to those cited above were deduced.

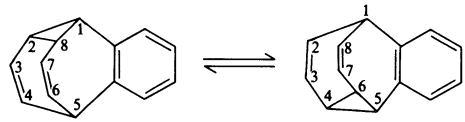
Oth and coworkers prepared the monohalogenobullvalenes and the fluoro compound **293** can exist in one of four locations shown[267]. The ^1H-NMR spectrum at $-60°$ C shows two absorptions at 5.89 and 2.38 ppm in a ratio 5.8 to 3.2. At 140° C the ^1H-NMR spectrum



(293–B) **(293–C)** **($293–O_b$)** **($293–O_c$)**

consists of one doublet at 4.48 ppm and the equivalent protons couple with fluorine with a mean value $J_{HF} = 6$ Hz. The ^{19}F-NMR spectrum at $-25°$C gives three absorptions (relative to CCl_3F) and the relevant populations are itemized in parentheses, δ 151.8 (78% B tautomer); 89.0 (7% O_b); 95.9 (15% O_c). It is apparent that fluorine eschews the cyclopropane position. The monochloro and monoiodobullvalenes show comparable behaviour. Bromobullvalene was studied earlier by the same group[268]. All three heavier halogens prefer residence at the vinyl position and examination of *t*-butoxy (and other alkoxy) bullvalenes indicates that the alkoxy groups prefer one or other of the vinyl carbons.

The variable temperature ^1H-NMR spectrum of the furan adduct of bullvalene and a survey of the chemistry of bullvalene is given in a review article[269]. The variable temperature NMR spectrum of benzobullvalene (**294**) indicates valence isomerization

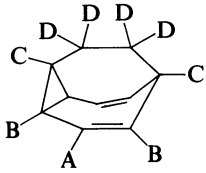


(a) **(b)**

(294)

between the tautomers **a** and **b**. A recent article on the scope of dynamic NMR spectroscopy includes a statistical analysis of the case of bullvalene[270].

The successful quest for bullvalene led to the investigation of a number of similar molecules. The fluxional behaviour of dihydrobullvalene (**295**) was apparent from its ^1H-NMR spectrum at room temperature[258]. This showed two 'type A' protons[271], which remain vinylic after Cope rearrangement, δ 5.63; for 'type B' δ 3.68. The 'type C' protons absorb at ca. δ 1.87 and overlap with the methylene protons. The observed coupling



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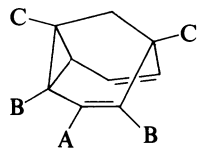
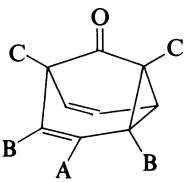


(296)

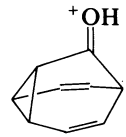
constants $J_{H_AH_B} = 7.5$, $J_{H_AH_D} = 1.7$ and $J_{H_BH_D} = 7.5$ Hz were determined. For the degenerate Cope rearrangement of **295** a value of $\Delta G^{\ddagger} = 9.5$ kcal mol^{-1} was found at $-40°$C[271, 272]; Merenyi and coworkers remarked that 'the valence isomerization of bullvalene is ca. 500 times slower'[259].

The hydrocarbon tricyclo[3.3.1.0^{2,8}]nona-3,6-diene(barbaralene), **296**, underwent rapid exchange between structures of equal energy such that at room temperature, the activation parameters were calculated[272, 274, 275].

A similarly rapid rearrangement at room temperature was observed for the corresponding nona-3,6-dien-9-one(barbaralone), **297**[257, 273]. The ^{1}H-NMR spectrum of **297** at

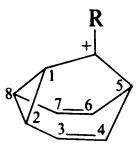


(297)

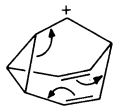


(298)

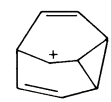
ambient temperature in CS_2 showed absorptions at δ5.69 (type A protons), 4.20 (type B), 2.60 (type C). A value $\Delta G^{\ddagger} = 9.6$ kcal mol^{-1} was determined for the degenerate rearrangement at $-55°$C[272, 276, 277]. Barbaralone is protonated in FSO_3H to give **298** at $-78°$C and here the activation barrier to rearrangement is markedly enhanced. No averaging process was observed prior to decomposition at $-5°$C; from this observation it is concluded that the lower limit to rearrangement is 13.8 kcal mol^{-1} [276, 277]. Since the barrier for rearrangement of protonated barbaralone is appreciably greater than that of the neutral ketone it was concluded that the positive charge inhibits the Cope rearrangement. Extrapolation to the 9-barbaryl cation would lead to the expectation of a still larger barrier for 9-barbaryl cations, e.g. **299**. By means of a precursor labelled with



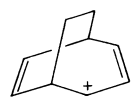
(299)



(299, R = H)



etc

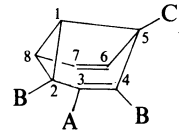


(300)

^{13}C in order to obtain a signal above the noise level, and also by means of the isotopic perturbation technique using octadeuterated and ^{13}C-labelled material, it was shown that ion **299** (R = H) underwent a sixfold degenerate process with $\Delta G^{\ddagger} = 3.8$ kcal mol^{-1} by

way of a series of divinylcyclopropylcarbinyl-ditto rearrangements the first step of which is indicated above for R = H[278]. A further rearrangement with a barrier ca. 5.0 kcal mol^{-1} higher, and mediated by **300** also occurs[277].

A very rapid degenerate Cope rearrangement was observed for tricyclo[3.3.0.0^{2,8}]octa-3,6-diene(semibullvalene), **301**. The ^{1}H-NMR spectrum showed type A protons at 5.08 ppm, type B at 4.17 ppm and type C at 2.97 ppm and was unchanged between $-110°$C and $+117°$C; three absorptions only were shown in the ^{13}C-NMR spectrum[279].



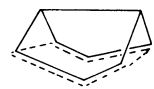
(301)

Anet, Meinwald and their coworkers froze out the degenerate Cope rearrangement in semibullvalene at $-160°$C and reported five ^{1}H and ^{13}C absorptions and these are shown in Table 18[280].

TABLE 18. Assignment of ^{1}H and ^{13}C chemical shifts in semibullvalene at $-160°$C (ppm)

δ	Atom	Atom	δ
2.79	H^2, H^8	C(2), C(8)	42.2
2.83	H^1	C(1)	48.0
3.16	H^5	C(5)	53.1
5.08	H^3, H^7	C(3), C(7)	121.7
5.59	H^4, H^6	C(4), C(6)	131.8

Line shape analysis of the ^{1}H-NMR spectrum yielded $\Delta H^{\ddagger} = 4.8 \pm 0.2$ kcal mol^{-1}; $\Delta G^{\ddagger} = 5.5 \pm 0.1$ kcal mol^{-1} at $-143°$C with $\Delta S^{\ddagger} = -5.4 \pm 3$ e.u. These very low activation parameters are supported by a value only slightly higher, $\Delta G^{\ddagger} = 6.4$ kcal mol^{-1} at $-141°$C found for octamethylsemibullvalene[272] and the low barrier to rearrangement derives from the short separation C(1)–C(5) in semibullvalenes. This brings about a lessening of the energy gap between a symmetrical bishomobenzene-like transition state and the less symmetrical ground state. There appears to be insufficient justification to sustain a postulate that semibullvalene in its ground state is itself a bishomobenzene structure (**302**);



(302)

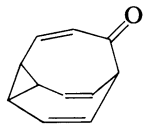
indeed the similarity in UV spectra between semibullvalene and dihydrobullvalene suggests[279] a classical structure for the former with a full cyclopropane ring and localized double bonds.

Recently the solid state ^{13}C-NMR spectrum of semibullvalene (m.p. $\sim -80°$C) was investigated below $\sim -90°$C. From a five line pattern at $\sim -185°$C, reversible

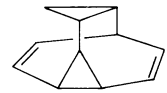
coalescence was almost achieved by −95°C. The barrier to rearrangement[281], $\Delta G^{\ddagger}$ = 5.5 kcal mol^{-1} at −133°C did not differ greatly from that determined in solution.

Octamethylsemibullvalene was synthesized by Anet and Schenk[272] and underwent degenerate rearrangement at −141°C with an activation energy of 6.4 kcal mol^{-1}.

Goldstein's group was able to synthesize homobullvalenone (**303**)[282]; within the temperature range (−60°–+120°C) studied, **303** was the only isomer related by Cope

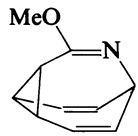


(**303**)



(**304**)

rearrangement. Homobullvalene (**304**), synthesized by de Meijere and Weitmeyer[283] was said to be a fluxional molecule from its ^{1}H-NMR spectrum.



(**305**)

Fluxional behaviour was shown by a number of azabullvalenes exemplified by **305** and the number of isomers is now dramatically lowered[284], since the N-atom is always located at a double bond and not at a cyclopropane ring.

XIV. INFRARED SPECTROSCOPY OF CYCLOPROPANES AND CYCLOPROPENES

The first comprehensive attempt to characterize cyclopropane rings by infrared spectroscopy appears to have been carried out by Bartelson and coworkers[285] in 1946 although King and coworkers addressed the question of the IR and Raman spectra of cyclopropane itself[286]. Absorptions in the region of 1025 and 865 cm^{-1} were taken as typical of cyclopropane rings, and in the particular case of 1,1,2-trimethylcyclopropane progressive purification of crude material led to a relative intensification of the above bands. The association of the latter absorption with a cyclopropane ring was disputed by Derfer and coworkers[287] who with numerous examples did however confirm the assertion that a band close to 1010 cm^{-1} is characteristic of a cyclopropane ring.

Although these ring absorption bands have a contentious history they are frequently cited in support of cyclopropane ring structures. Simmons and coworkers[288] report that the absorption at 1020 cm^{-1} is generally absent in hexasubstituted compounds and is prone to being obscured by the presence of carbon–oxygen bonds. This band at 1020 cm^{-1} has been assigned by Herzberg to a symmetric vibration of the cyclopropane ring[289].

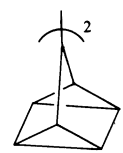
The C–H stretch in cyclopropanes, i.e. where the hydrogen is bonded to the cyclopropane carbon, was noted to occur in a relatively free region at slightly higher frequency than 'normal' C–H stretches. From analysis of a large number of compounds the cyclopropane C–H stretching absorption was stated to lie in the range 3095–3012 cm^{-1} [290] and also the rather larger range 3125–2855 cm^{-1} was also cited[291]. Cole[292] also

reported from a study of steroids and terpenoids that the absorption in the range 3040–3058 cm^{-1} could be of diagnostic value when the three-membered ring contained a CH_2 group. Josein had arrived at a broadly similar result from an incompletely resolved band[293].

A further development in the characterization resulted from a study of the near infrared region, by Washburn and Mahoney[294] who showed that the first overtone of the cyclopropyl C–H stretching frequency absorbs at 6097 cm^{-1}, with a combination band also present at ca. 4465 cm^{-1}. The overtone band is sharp though weak and separated from the first overtone of the saturated aliphatics. Any possible ambiguity with terminal methylene groups can be removed in infrared spectroscopic terms by analysis of the fundamental of the methylene.

A range 6250–5952 cm^{-1} for this overtone was observed by Gassman and Zalar[295] and a correlation of the frequency with Taft's σ^* constant was found with higher frequency absorptions being observed for more strongly electron-withdrawing substituents. An extensive tabulation of stretching frequencies of the first overtones of the C–H fundamentals in cyclopropane rings was given. Two further compilations of data have been presented. In one of these Weitkamp also cites extinction coefficients; in the particular case of dicyclopropylmethane, overtone and combination bands with extinction coefficients (ε) in parentheses are 6097 cm^{-1} ($\varepsilon = 1.10$) and 4482 cm^{-1} ($\varepsilon = 4.33$). The ratio of extinction coefficients is 3.94 with values ranging 2.16–6.14. Corresponding data for olefins and aromatic rings which may cause confusion are also given[296]. The other tabulation of data is presented by Simmons and coworkers[288].

In diquadricyclene, **306**, whose infrared spectrum is shown[297], the cyclopropyl C–H stretch (in CCl_4) appears at $\nu_I = 3072$ cm^{-1} ($\varepsilon = 165$) and 3048 cm^{-1} (shoulder). The first overtone of the ν_I band was located at 6020 cm^{-1} ($\varepsilon = 4.4$) and in addition a second



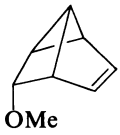
(306)

overtone occurred at 8850 cm^{-1} ($\varepsilon = 0.24$). For 4-tricyclanol (**66**) (X = OH) (in $CDCl_3$) the first overtone occurred at 5985 cm^{-1}[298]. This value has recently been redetermined in CCl_4 to be 3053.6 cm^{-1} and values for other 4-substituted tricyclenes were determined[299]. These were X = H, 3053.1; X = CO_2H, 3056.0; I, 3056.1; Cl, 3057.3; NO_2, 3063.8; NHCOOMe, 3055.1; CH_2OH, 3053.9; COO^- $^+N(Bu\text{-}t)_4$, 3043.7 cm^{-1}. There is an obvious trend here in that the most strongly electron-withdrawing substituent causes absorption at highest frequency; such is also the case with 4-substituted camphors[300]. However, the point for tricyclene itself (**66**) (X = H) is inexplicably deviant[299].

Skattebøl cited a number of examples including spiropentane (**67**) for which the absorption of the C–H overtone was 6082 cm^{-1} ($\varepsilon = 1.20$); the larger value of ε is regarded as an indication of the greater number of methylene groups[136].

In the highly strained compound **307** in which all four valencies at the bridgehead carbon are constrained within a hemisphere the first overtone absorbs at 6072 cm^{-1} ($\varepsilon = 0.237$)[301]; the compound **308**, also highly strained, shows the overtone at 6020 cm^{-1} (fundamental 3040 cm^{-1}) (cyclopropyl ring vibrations 810 and 795 cm^{-1})[302].

(307)

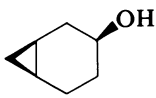


(308)

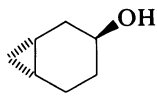
Although absorption bands assigned to cyclopropane ring vibrations are sometimes said to be of questionable significance, to be occluded or apparently absent, they have nevertheless been cited consistently in support of cyclopropane structures. A limited number of examples will be given.

Wynberg's group reported cyclopropyl C–H stretch in dehydroadamantane at 3030 cm^{-1} and also absorption at 1030 and 830 cm^{-1}, not present in the starting material adamantane[303].

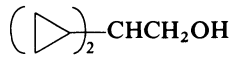
Hanack's group has reported IR data on a large number of compounds from which one may give by way of example, in addition to the cyclopropyl CH stretch near 3000 cm^{-1}, absorptions for **309** at 810 cm^{-1}, for **310** at 1013 cm^{-1} and for **311** at 1015 and 820 cm^{-1} [304, 305]. Other examples included 3080 and 1020 cm^{-1} for **312** and 3095, 1021



(309)



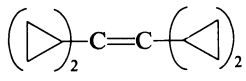
(310)



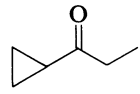
(311)

and 818 cm^{-1} for **313**[306, 307]. The gas phase IR spectrum af asterane (**314**) gave bands at 3032 and 3019 cm^{-1} together with relatively weak ring deformation bands at 1043, 958 and 890 cm^{-1} [308].

Recently Wiberg's group has described synthesis of a number of highly strained compounds exemplified by **91** whose IR spectrum (CS_2) showed the CH stretching bands at 3069 and 3006 cm^{-1}, together with an absorption at 1093 cm^{-1} (CCH bending) and a



(312)



(313)

(314)

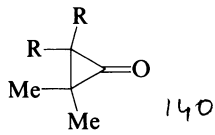
strong band at 603 cm^{-1}, attributed to an antisymmetric CC stretch[87]. This very intense low frequency absorption seems to be characteristic of highly strained propellanes and in **315**[309] appears at 574 cm^{-1}; in addition **315** shows the cyclopropyl CH stretch at 3050 cm^{-1} and the 'normal' cyclopropane ring deformation at 1101 cm^{-1} [310].

(315)

(316)

Wiberg and coworkers proposed that the intense low frequency absorption, which occurs in a region containing skeletal vibration deformation of (usually) negligible intensity may be indicative of unusual charge distribution in small ring propellanes[311] and MNDO calculations predict the high intensity of this band in these strained molecules[312]. Two further examples were reported; for **316** the relevant absorptions occurred at 3056 and 2997 cm^{-1}, 1044 and 906 cm^{-1} and the low frequency band at 530 cm^{-1}, the corresponding bands for **307** were 3065 and 2989 cm^{-1}, 1030 and 955 cm^{-1} and 515 cm^{-1}[309].

Cyclopropanone gave a carbonyl absorption at 1825 cm^{-1} at 20 K[313] and in CH_2Cl_2 solution bands were subsequently reported at 3045 cm^{-1} (C–H) and 1813 cm^{-1}[314]. The high frequency of the carbonyl stretch is testimony to the large strain inherent in this



140

(**317**, R = Me)
(**318**, R = H)

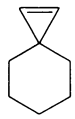
compound. In tetramethylcyclopropanone (**317**) frequencies of 1843 and 1823 cm^{-1} were determined and for **318**, in addition to an absorption at 3050 cm^{-1} (C–H stretching), the value ν_{co} = 1815 cm^{-1} was also observed[315].

XV. INFRARED SPECTROSCOPY OF CYCLOPROPENES

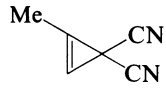
A review of infrared (and Raman) spectra of cyclopropenes has been presented[163] (see also Ref. 316). In cyclopropene itself a weak symmetrical stretch (A_1) involving the vinyl hydrogens occurs at 3076 cm^{-1} and it was proposed that the C–H stretching vibrations that involve the methylene carbons of cyclopropene should approximate to those of cyclopropane.

Cyclopropene shows a double bond stretch of medium intensity at 1641 cm^{-1}. However this description is less than adequate since especially in rigid ring systems, quite strong coupling of all the ring bonds occurs and an isolated double bond vibration is not observed, although the term 'double bond stretching frequency' is common usage. The frequency of the formal double bond stretch is rather sensitive to substitution as shown by the data in Figure 3 and as noted in some relatively early work on sterculic acid derivatives[318].

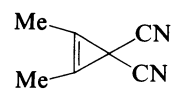
Closs proposed that the large exocyclic angle ~ 150° in cyclopropene will result in a more pronounced coupling of the skeletal vibrations with those of substituent bonds than is the case for other olefins[163, 316]. Such a coupling is expected to shift the ring vibration to higher frequency in accord with the finding that coupled oscillators vibrate at frequencies further apart from each other than expectations based on an uncoupled model would indicate.



(**319**)



(**320**)



(**321**)

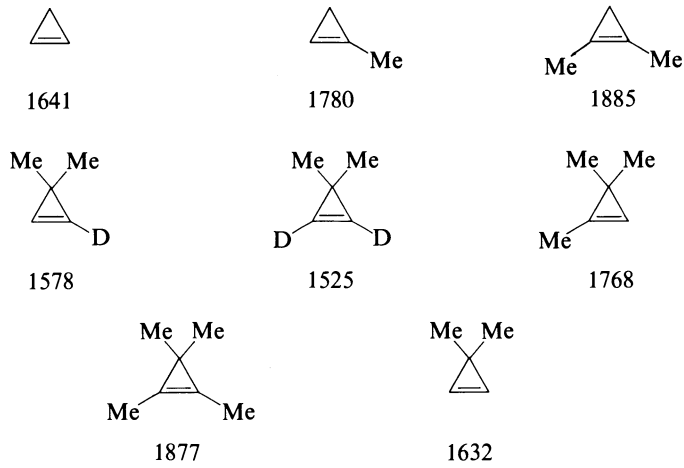


FIGURE 3. Double bond stretching frequencies (in cm^{-1}) of substituted cyclopropenes[152, 316, 317]

More recent examples of the cyclopropene 'double bond' stretch are relevant. Denis and coworkers reported $\nu_{C=C} = 1625\ cm^{-1}$ for **319** and 1635 cm^{-1} for **161**; a slightly higher value, 1670 cm^{-1}, was observed for **149** and here again progressive methylation of **149** to give **320** and **321** brings about a higher frequency[318].

Examination of the IR spectra of halogen-substituted cyclopropenes data in Figure 4,

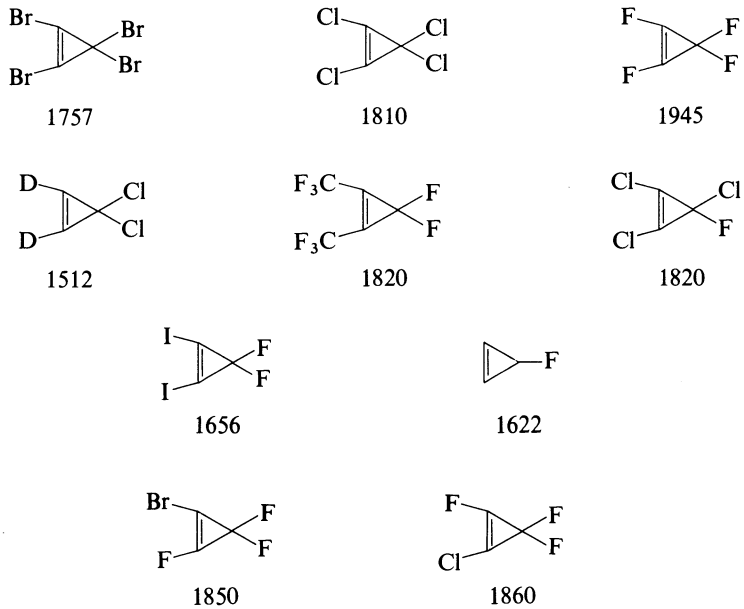
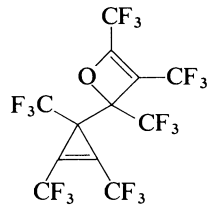


FIGURE 4. Double bond stretching frequencies of halogenated cyclopropenes (in cm^{-1})[214, 220, 222, 319–321, 326]

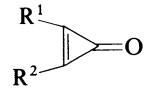
shows clearly that progressively greater substituent electronegativity increases the 'double bond stretching' frequency. The value of 1945 cm^{-1} is the highest recorded cyclopropene stretching frequency.



(322)

The vapour phase IR spectrum of **229**[244] gave a double bond absorption at 1912 cm^{-1} and Kobayashi's group reported a value of 1900 cm^{-1} for the trifluoromethyl derivative **322**[218].

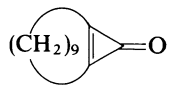
(323)



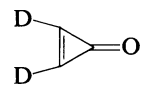
(324, $R^1 = R^2 = Me$)

The IR spectrum of **323** resembles cyclopropene, and the double bond stretch appears at 1663 cm^{-1}; dimethylation again results in a shift to higher frequency, 1923 cm^{-1} [322]. It was also shown that successive introduction of two deuterium atoms into **323** reduced the frequency to 1611 and 1567 cm^{-1}.

Cyclopropenone (**163**) was first isolated as a pure liquid in 1972[323], though substituted derivatives **168** and **324** that were reported earlier showed ν_{max} = 1838 and 1605 cm^{-1} for **168**; 1848, 1660 and 1657 cm^{-1} for **324**[324]; for **325**[325] values of ν_{max} were 1830 and 1630 cm^{-1}.



(325)



(326)

Cyclopropenone and its dideuterio equivalent **326** were subjected to rigorous infrared and Raman spectral analysis. Rather than the higher values reported above, the formal 'C=C stretch' was found to be at 1483 cm^{-1} in cyclopropenone and at 1409 cm^{-1} in **325**. In addition these compounds have higher frequency bands at 1840 cm^{-1} and 1780 cm^{-1} respectively[326]. In preference to specific attribution to localized vibrations, a more accurate description of these absorptions is that they are out-of-phase and in-phase mixtures of the C=O and C=C stretches together with 'some contribution' from the symmetric C=C stretch.

A normal coordinate analysis of the IR spectrum of cyclopropenones executed slightly later by the same group confirmed that the C=O and C=C stretches are indeed mixed. The marked difference between the apparent 'C=C' stretching frequencies in cyclopropenone

and in **326** considered together, ca. 1450 cm^{-1}, and those of disubstituted cyclopropenones, ca. 1650 cm^{-1}, is calculated to be due almost entirely to a mass effect[327].

XVI. INFRARED SPECTROSCOPY OF CYCLOPROPENIUM IONS AND CYCLOPROPYNE

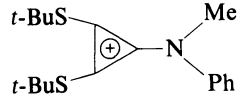
The first reports of the IR spectra of cyclopropenium ions were those of Breslow's group[328] who for the parent ion **173** reported absorptions at 3105 cm^{-1} (C–H stretch), 1276 cm^{-1} (C–C stretch), 908 cm^{-1} (C–H in-plane bend) and 736 cm^{-1} (C–H out-of-plane bend). The four bands were in accord with a D_{3h} structure. All absorptions were moved to lower frequency, i.e. 2327, 1239, 665 and 542 cm^{-1} in the fully deuterated ion. For the corresponding $C_3Cl_3^+$ ion C–C and C–Cl stretches were at 1312 and 735 cm^{-1} while in the $C_3Br_3^+$ ion the C–C and C–Br stretching frequencies were at 1276 and 575 cm^{-1}.

Yoshida and coworkers reported the A_1' (Raman active) and E^1 (Raman and IR active) vibrations of a number of cyclopropenium ions (Table 19)[329]. The nature of the substituent effects led to the suggestion that the variation in frequency is due to an electronic effect of the substituent, since if a mass effect of the substituent were dominant the sequence of shifts to higher frequency would be H < Me < NMe_2 < Cl[329]. Some IR and Raman spectra of cyclopropenium ions are shown in a review by Schrader[330].

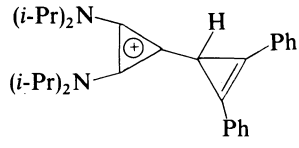
TABLE 19. Vibrations of substituted cyclopropenium ions C_3X_3 (in cm^{-1})

X	A_1'	E^1
Me_2N	1985	1553
Me	1880	1490
Ph	1845	1411
Cl	1791	1312

In a triferroxenylcyclopropenium ion (as ClO_4^- salt) the IR spectrum exhibits a very intense band at 1494 cm^{-1}, attributable to the E^1 unsymmetric degenerate stretching vibration of the cyclopropenium ring; a strong band was also present at 1100 cm^{-1} [194].



(327)



(328)

At a phenomenological level the absorptions of cyclopropenium rings have been determined by several groups. Yoshida noted an absorption at 1837 cm^{-1} in **327**[331] and the spectrum of **183** was entirely dominated by 'an intense broad band at ca. 1200 cm^{-1},'[332]. In **186** bands of medium intensity at 1895 and 1880 cm^{-1} were cited together with a strong band at 1570 cm^{-1}, and for **328** a medium intensity absorption at 1835 cm^{-1} together with a very strong absorption at 1535 cm^{-1} were noted[333].

Craig and coworkers noted strong bands at 1946 cm^{-1} (C–C stretch) and 1394 cm^{-1}

(symmetric CCC stretch) for the ion $C_3F_2H^+$; the monodeuterio analogue was also considered and force constants estimated[334].

Whereas singlet cyclopropyne is calculated to be merely a transition state for the degenerate rearrangement of propadienylidene (CH_2=C=C:), triplet cyclopropyne is thought to be a minimum on the potential energy hypersurface. The 'triple bond' stretching frequency is calculated as 2050 cm^{-1} in the singlet structure and the 'double bond' stretching frequency is calculated as 1920 cm^{-1} in the triplet. Other frequencies are also calculated[335].

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CHAPTER **4**

The chemistry of ionized cyclopropanes in the gas phase

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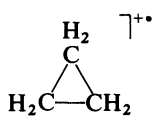
I. INTRODUCTION

The gas phase ion chemistry of small ring compounds, particularly of cyclopropane and its derivatives, has been a subject of growing interest in recent years. Techniques such as conventional mass spectrometry (MS), gas phase radiolysis, ion cyclotron resonance (ICR) spectroscopy, photodissociation, collisional activation (CA) mass spectrometry and field ionization kinetics (FIK) have been used, sometimes in conjunction with classical labelling studies, to probe the chemistry of these remarkable species in the time regime of 10^{-11} to 10^{-1} seconds. Moreover, as these experiments are executed on the isolated molecules (i.e.

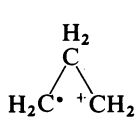
in the absence of solvents or counter ions), they are ideally suited for comparison with theoretical studies which, usually, describe the isolated molecules. Indeed, numerous examples dealing with quite diverse topics that demonstrate the advantages of combined experimental/theoretical investigation for gaseous ion studies have been described in the literature[1]. In this article, some examples related to the gas phase chemistry of ionized cyclopropanes will be discussed in detail by using this very approach. Special emphasis is given to the various aspects of the cyclopropane cation radical itself (Section II) and to the detailed mechanism of ring-opening and further isomerization of open- and closed-shell cyclopropane ion derivatives, which in many cases precede the unimolecular dissociation (Section III). The role of cyclopropanes as intermediates in rearrangement/dissociation processes is dealt with in Section IV, and problems related to the chemistry of cyclopropyl cations are briefly mentioned in Section V. Some aspects of the gas phase chemistry of negatively charged cyclopropanes are discussed in Section VI, and in the concluding Section VII the gas phase chemistry of ionized cyclopropenes is surveyed. It should be emphasized that this chapter will not focus on the role that analytical mass spectrometry may play in elucidating structural problems; treatises of this kind may be found in textbooks on organic mass spectrometry. Similarly, it is not intended to discuss any experimental techniques in detail; although references will be made to them when appropriate.

II. THE CYCLOPROPANE CATION RADICAL

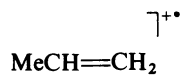
Various isomers of the $C_3H_6^{+\cdot}$ cation radical, in particular **1–3**, have been studied extensively by both experimental[2–15] and theoretical[16–18] methods. According to the most recent calculations[18] the ground state potential energy surface of ionized cyclopropane (**1**) shows a relatively flat pseudorotation region with three symmetrically equivalent saddle points, three further symmetrically equivalent saddle points of another type, and six symmetrically equivalent minima. The two saddle points correspond to a chemical structure which is best described as a trimethylene having two two-electron and one one-electron C–C bond (**2**) and also to a structure, which can be viewed as a π-complex of ethylene with ionized carbene, as shown in **4**. The actual minima in the lower surface, i.e. **1**, is a scalene triangle which is approximately halfway between **2** and **4**. The total change in energy along the pseudorotation path was calculated to approximately 7 kcal mol^{-1}. The first excited $^2A'$ surface does not show a pseudorotation region but has three relatively deep, symmetrically equivalent minima which correspond to a fully open-ring trimethylene cation radical isomer, with a one-electron *anti*-bond between the two open ends. According to the calculations, both surfaces are separated by as much as 1.3 eV (29.9 kcal mol^{-1}). Since the ring-opening **1** → **2** is the first step in the isomerization **1** → **3**, the calculations suggest that the cation radicals of 'cold' cyclopropane and propene should exist as distinctly different ions in the gas phase. This has been confirmed by collisional activation measurements[10,11,14], which clearly show that **1** and **3** do indeed exist as stable $C_3H_6^{+\cdot}$ species. Isomers initially formed as $CH_2CH_2\dot{C}H_2$ (via CH_2O loss from tetrahydrofuran) isomerize largely to **1**, and ions initially formed as $Me_2C^{+\cdot}$ (from 1,1-dimethylcyclopropanes)[19] isomerize via 1,2 hydrogen migration to **3**.



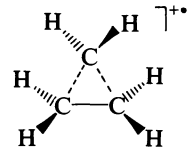
(1)



(2)



(3)



(4)

A most careful study to probe experimentally the effect of internal energy on the structure and reactivity of ionized cyclopropane was recently published by Lias and Buckley[15]. They generated $C_3H_6^{+\cdot}$ by charge transfer to cyclopropane from $C_6F_6^{+\cdot}$ (recombination energy, RE, 9.91 eV), $CS_2^{+\cdot}$ (RE = 10.08 eV), $COS^{+\cdot}$ (RE = 11.18 eV), and $Xe^{+\cdot}$ (RE = 12.12 eV).

From determination of the charge transfer equilibrium constant in the c–C_3H_6 : C_6F_6 mixture, the long questioned value for the 300 K ionization energy of cyclopropane of 9.86 eV has been obtained in satisfying agreement with the results of *ab initio* calculations[18] (IE = 9.8 eV) and photoionization and photoelectron experiments (9.8–10.06 eV)[20–23]. Moreover, the characteristics of the ion/molecule reactions of the so obtained $C_3H_6^{+\cdot}$ ions with various neutral molecules (NH_3, PH_3 and other bases) showed a strong dependence on the internal energy of the former. $C_3H_6^{+\cdot}$ ions generated with internal energy < 1.3 eV exhibited a reactivity which was interpreted as typical for ring-closed $C_3H_6^{+\cdot}$, i.e. the condensation reactions[6] 1 and 2

$$c\text{-}C_3H_6^{+\cdot} + NH_3 \rightarrow CH_2NH_2^+ + C_2H_5^{\cdot} \quad (1)$$

$$c\text{-}C_3H_6^{+\cdot} + NH_3 \rightarrow CH_2NH_3^{+\cdot} + C_2H_4 \quad (2)$$

In contrast, ions with internal energy > 1.3 eV underwent isomerization to ionized propene to a substantial extent (up to 80%). Thus, the barrier E° for the isomerization **1** → **3** is indeed in the range $1.3 \leqslant E^\circ < 1.6$ eV, as predicted by theory. The upper value is derived from the fact that, since the $C_3H_6^{+\cdot}$ ions undergoing dissociation to $C_3H_5^+ + H^{\cdot}$ in either **1** or **3** have a common structure, the barrier to ring opening must lie at or below the onset for this process (11.44 eV), i.e. the barrier must be $E^\circ \leqslant 11.44 - 9.8$ eV.

A detailed comparison of the energetics of the rearrangement of neutral and ionized c-C_3F_6 and $CF_3CF{=}CF_2$ with that of cyclopropane and propene, respectively, was performed by Beauchamp *et al.*[24] using infrared multiphoton dissociation mass spectrometry in conjunction with thermochemical data. They arrive at the conclusion that at all energies used the entire c-$C_3F_6^{+\cdot}$ molecular ion population had isomerized to the more stable $CF_3CF{=}CF_2^{+\cdot}$ structure. Noteworthy are the facts that, whereas c-$C_3H_6^{+\cdot}$ and $MeCH{=}CH_2^{+\cdot}$ are prevented by a high barrier (> 1.3 eV) from a facile interconversion, the barrier for the analogous process of the perfluorinated system is much lower ($E^0 < 0.3$ eV). Moreover, the *reacting* configuration for $H^{\cdot}$ loss from $C_3H_6^{+\cdot}$ is represented by the propene cation radical (**3**) whereas the minimal energy requirement path for $C_3F_6^{+\cdot}$, i.e. loss of CF_2, involves ionized perfluorocyclopropane (**5**) as the actual starting species. In other words, dissociations of either **1**/**3** or **5**/**6** are preceded by ring-opening/recyclization processes. Relevant parts of the potential energy diagram for both systems are depicted in Figure 1.

III. ISOMERIZATION/DISSOCIATION PROCESSES OF IONIZED CYCLOPROPANES

A. Ring-opening of Substituted Cyclopropane Cation Radicals

As already mentioned in the previous paragraph, ionized cyclopropanes may well undergo ring-opening provided that the internal energy is high enough to overcome the isomerization barriers. This is a situation found not only for the parent hydrocarbon system, i.e. c-$C_3H_6^{+\cdot} \rightleftharpoons MeCH{=}CH_2^{+\cdot}$, but also for many cyclopropane derivatives. Moreover, for decomposing ions, whose internal energy is always higher than the one for non-decomposing species, it is highly likely that quite often isomerization will precede dissociation. A striking example is provided by $C_4H_5N^{+\cdot}$ ions whose unimolecular decompositions were studied by using the photoion-photoelectron coincidence (PIPECO)

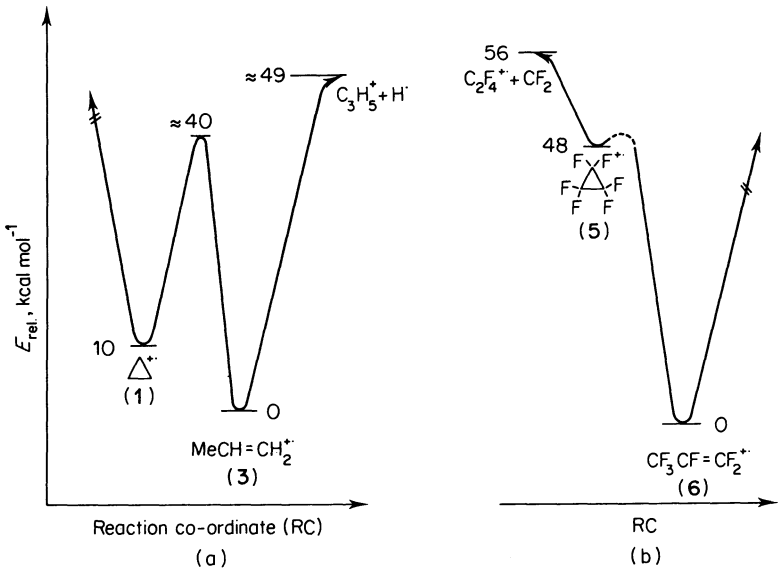
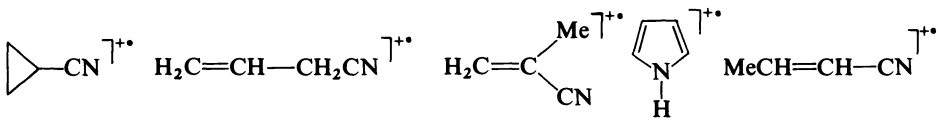


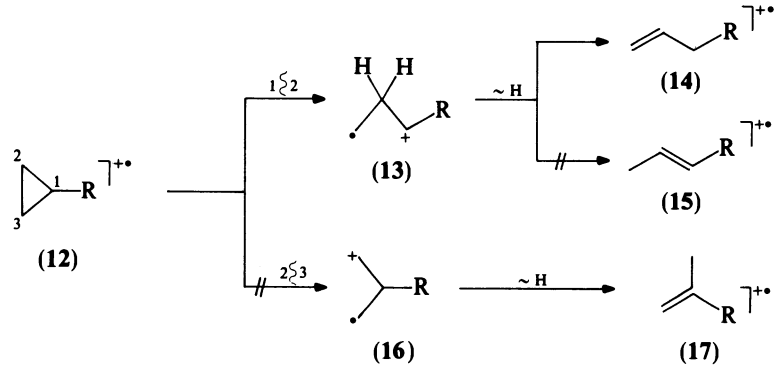
FIGURE 1. Potential energy diagram for (a) $C_3H_6^{+\cdot}$ and (b) $C_3F_6^{+\cdot}$ isomers

technique[25]. On the basis of these measurements, together with molecular orbital calculations, Willett and Baer[26] concluded that, prior to fragmentation the molecular ions of cyclopropyl cyanide (**7**), allyl cyanide (**8**), methacrylonitrile (**9**) and pyrrole (**10**) rearrange to one common radical ion, most likely that of pyrrole (**10**). In contrast, ions having much less internal energy and which were characterized by their specific ion/molecule reactions and their photodissociation kinetics were found to behave differently[27]: **9** and **10** retain their structural integrity, whereas 15% of **7** rearranges to **10**, and ionization of allyl cyanide gives rise to three ionic species: **8** (25%), **10** (30%) and ionized crotononitrile **11** (45%).



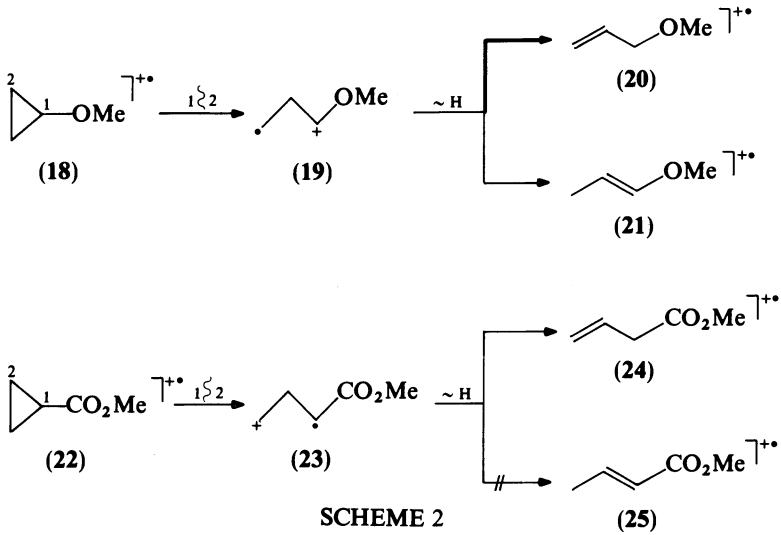
(7) (8) (9) (10) (11)

Insight into the mechanistic details of the ring-opening of ionized cyclopropanes has been obtained by using various techniques and studying quite a number of substrates. For example, the molecular ions of alkyl-substituted cyclopropanes (**12**) were found to undergo specific cleavage of the C(1)–C(2) bond, followed by hydrogen migration, to give rise to the ion radicals of terminal olefins **14**[28,29]. Using field ionization kinetics[30] it could be demonstrated that the isomerization **12** → **14** is completed after approximately $t \sim 10^{-9}$ s. Collisional activation[31] mass spectrometry further reveals that the possible isomers **15** and **17** were not generated from **12**, thus excluding both the cleavage of the C(2)–C(3) bond of **12** (**12** → **16**) and the hydrogen transfer process **13** → **15** (Scheme 1). The isomerization **16** → **17** is open to question.



SCHEME 1

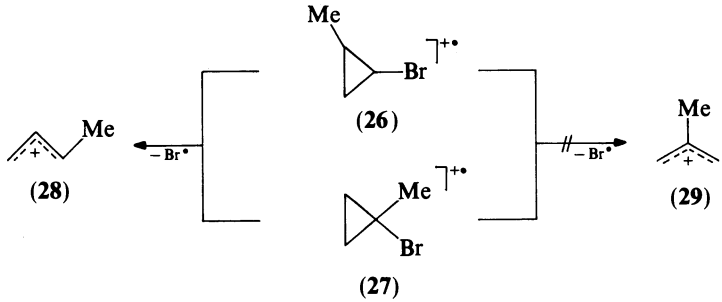
By using similar techniques Schwarz, Levsen and coworkers[32] studied the very complex isomerization pattern of methoxy and carbomethoxy substituted cycloalkanes (three to seven-membered rings). This study was prompted by the well-known effects that substituents exert on the course and reactivity of the ring-opening of *neutral* cyclopropane derivatives upon hydrogenolysis[33] or bromination[34]. It was observed that, although the extent of isomerization depends on both the ring size and the nature of the substituent, irrespective of the latter, ring-opening involves *exclusively* the C(1)–C(2) bond whereby *linear* alkene cation radicals were formed. The position of the double bond in the olefin eventually generated, however, is determined more by the ring size of the precursor molecules than by the electronic properties of the substituent. In the present context it is of interest only to mention that ionized methoxycyclopropane (**18**) preferentially isomerizes (via **19**) to **20** and to a minor extent to **21**; the cation radical of the carbomethoxy derivative **22** was found to isomerize exclusively to **24** and not to the thermochemically more stable α, β-unsaturated ester **25** (Scheme 2). This is reminiscent of the behaviour of **12** (R = alkyl),



SCHEME 2

which also gives exclusively 1-olefin cation radicals and it remains to establish the origins of these subtle substituent effects.

The chemistry of polysubstituted cyclopropane cation radicals seems also to be governed by processes comparable to the ones outlined in Schemes 1 and 2. For example, electron impact ionization of either 1,2-disubstituted (**26**) or 1,1-disubstituted cyclopropane (**27**) leads to the elimination of the Br· radical[35]. From the CA mass spectra of the resulting $[M-Br]^+$ ions and those of $C_4H_7^+$ ions generated from other suitable precursors it must be concluded that both **26** and **27** give only the 1-methylallyl cation **28**, and not the isomeric 2-methylallyl cation **29** (Scheme 3).

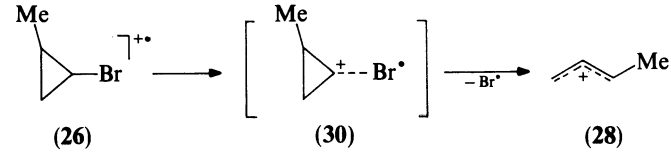


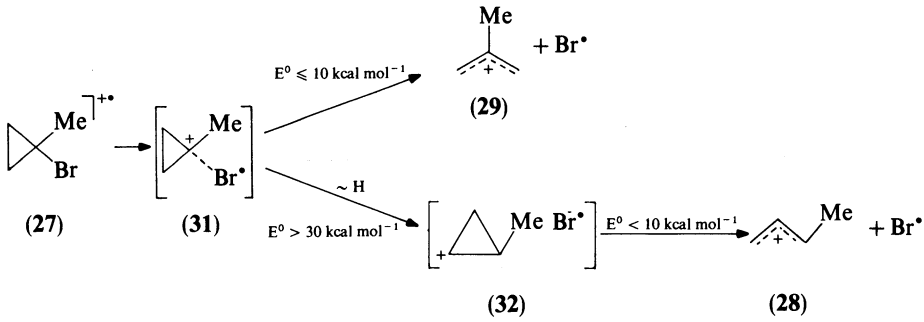
SCHEME 3

At first sight the formation of **28** from **26** might be explained by a mechanism in which stretching of the (C–Br) bond is coupled with a symmetry-allowed disrotatory ring opening of the incipient Br· solvated 2-methylcyclopropyl cation (**30**) to give the $C_4H_7^+$ product **28**. However, this mechanism (Scheme 4) is at most of a minor importance for the dissociation of **26**, as will be shown later. An analogous mechanism for Br· loss from **27** would result in the formation of the wrong isomer **29**, but not of the required structure of **28**. Formation of the latter may be conceivable only if the activation energy for the ring-opening of the incipient 1-methylcyclopropyl cation (**31**) to give **29** is higher than the energy required for a combined process of a 1,2-hydride shift (**31** → **32**), followed by symmetry-allowed ring-opening to **28**. However, quantum mechanical molecular orbital calculations carried out at both a semi-empirical (MNDO) and an *ab initio* level (STO-3G//4-31G) clearly indicate that such an order of activation energies is not met[35]. Thus, the experimentally established formation of a 1-methylallyl cation (**28**) must proceed via a reaction pathway which is fundamentally different from all the alternatives discussed so far. In fact, calculations on the chlorine analogues of **26** and **27** reveal that ring-opening followed by a 'hidden' hydrogen rearrangement[36] accounts for halogen loss from ionized cyclopropane derivatives.

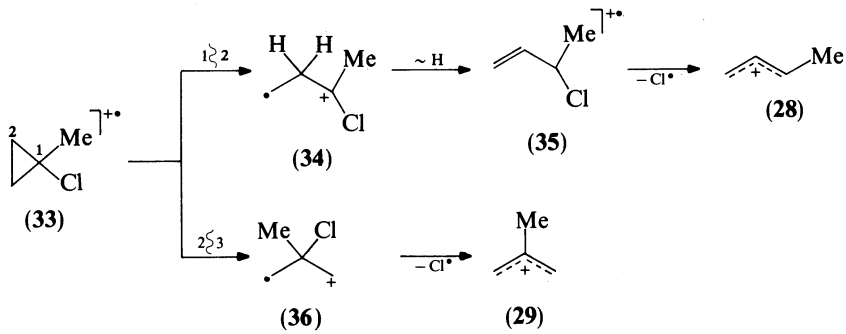
The minimal energy requirement path (MERP) as calculated by MNDO for Cl· loss from the cation radical of **33** excludes direct halogen loss as an energetically favoured pathway. In contrast, **33** which is not found to exist in a potential minimum on the level used, undergoes spontaneous ring-opening, thus giving rise to the formation of either **34** or **36**, which may then further react according to Scheme 5. The calculations indicate, that the reaction sequence **33** → **34** → **35** → **28** requires 21 kcal mol^{-1} *less* than the alternative path **33** → **36** → **29**.

Part of the (two-dimensional) potential energy diagram for the isomerization and decomposition reactions of **33** is shown in Figure 2. Obviously, the multistep pathway **33** → **34** → **35** → **28** (Scheme 5) represents the energetically most favoured reaction channel. Noteworthy is the fact that direct Cl· elimination from the ring-opened





SCHEME 4



SCHEME 5

intermediate **34** is extremely unlikely to occur. The calculations reveal that continuous stretching of the (C–Cl) bond of **34** proceeds via a transition state, which formally corresponds to a cationic carbene with a weak interaction with Cl˙. ΔH_f^0 of this complex is as high as 340 kcal mol^{-1}, and its collapse would result in the formation of the 1-methylcyclopropyl cation (**37**).

Similar computational results were obtained for ionized 1-chloro-2-methylcyclopropane (**38**). The calculations indicate that two energetically comparable pathways can account for the formation of the 1-methylallyl cation (**28**). One involves a multistep reaction commencing with spontaneous cleavage of the C(1)–C(2) bond of **38**, followed by hydrogen migration (**39** → **40**) and terminated by Cl˙ loss. The highest point on the reaction coordinate has an energy of approximately 255 kcal mol^{-1}. This is comparable in energy with the transition state energy for direct loss of Cl˙ from the intermediate **41**. The reaction sequence **38** → **42** → **43** → **29** is, however, by as much as 12–14 kcal mol^{-1} higher in energy than the processes discussed, which might be sufficient to prevent **38** from dissociating to **29**, in agreement with the experimental observations.

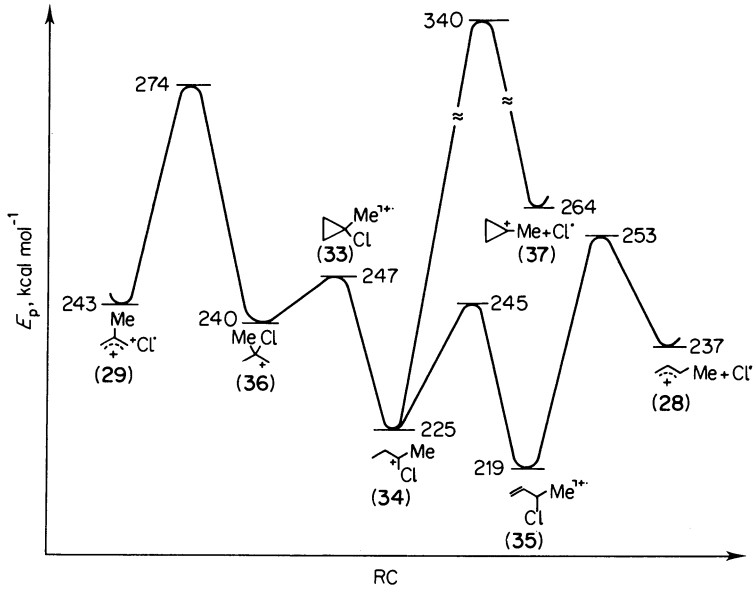
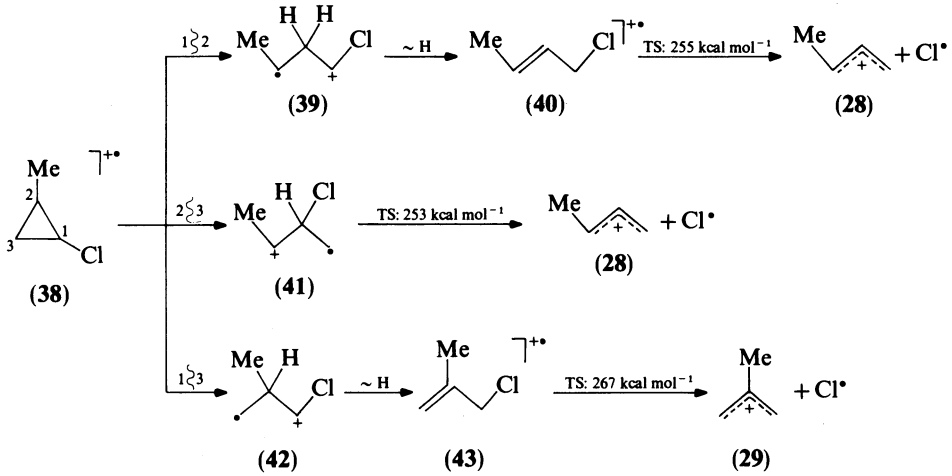


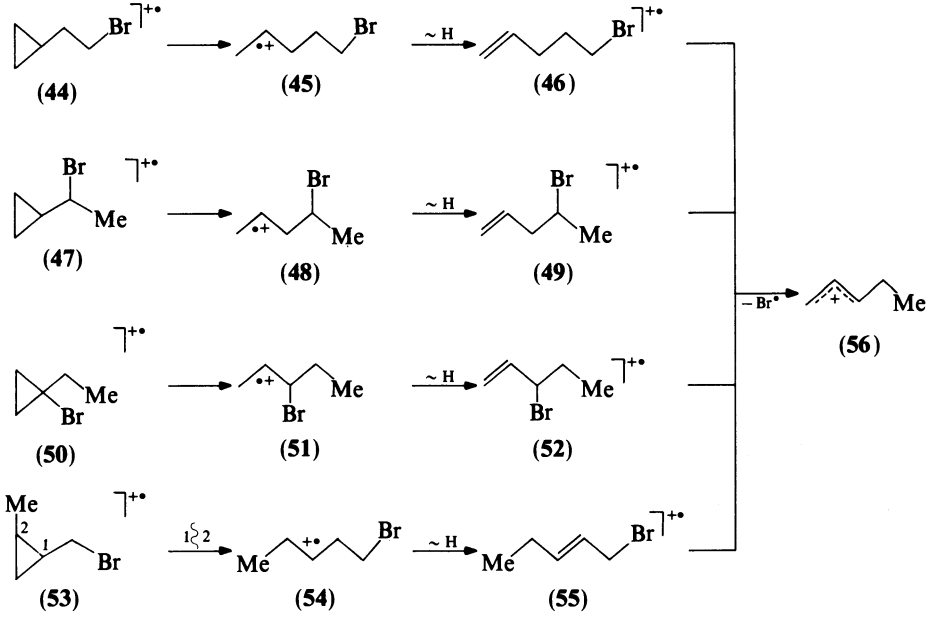
FIGURE 2. Potential energy diagram (MNDO) for isomerization and dissociation of ionized 1-chloro-1-methylcyclopropane (33)



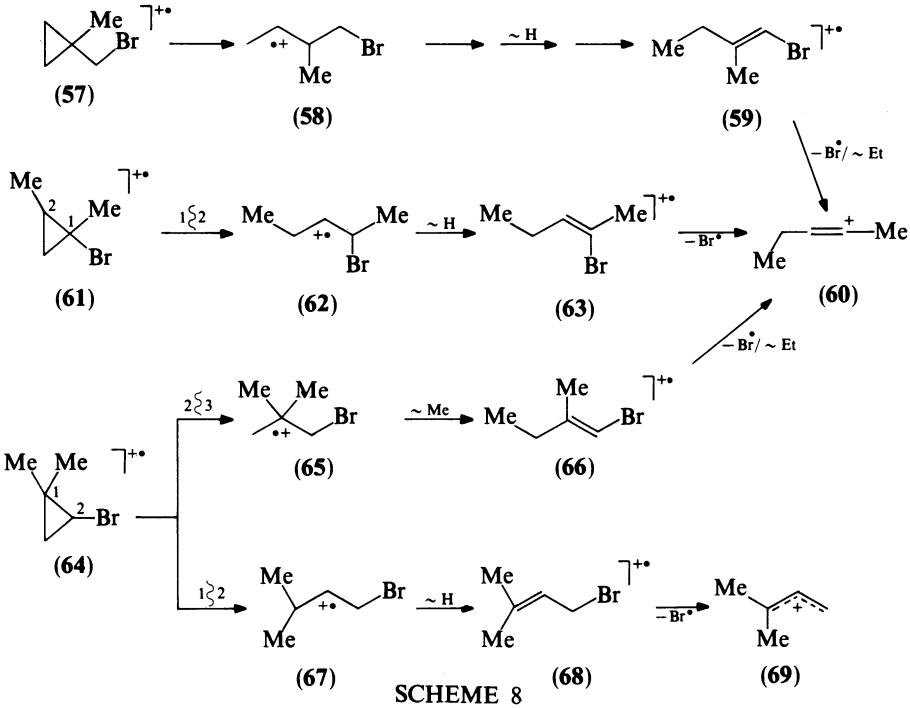
SCHEME 6

In a similar study it has been established that the gas phase chemistry of isomeric C_5H_9Br (of which a total of 31 isomers were investigated[37]) is, for the substituted cyclopropanes, characterized by multistep reactions, commencing with ring opening.

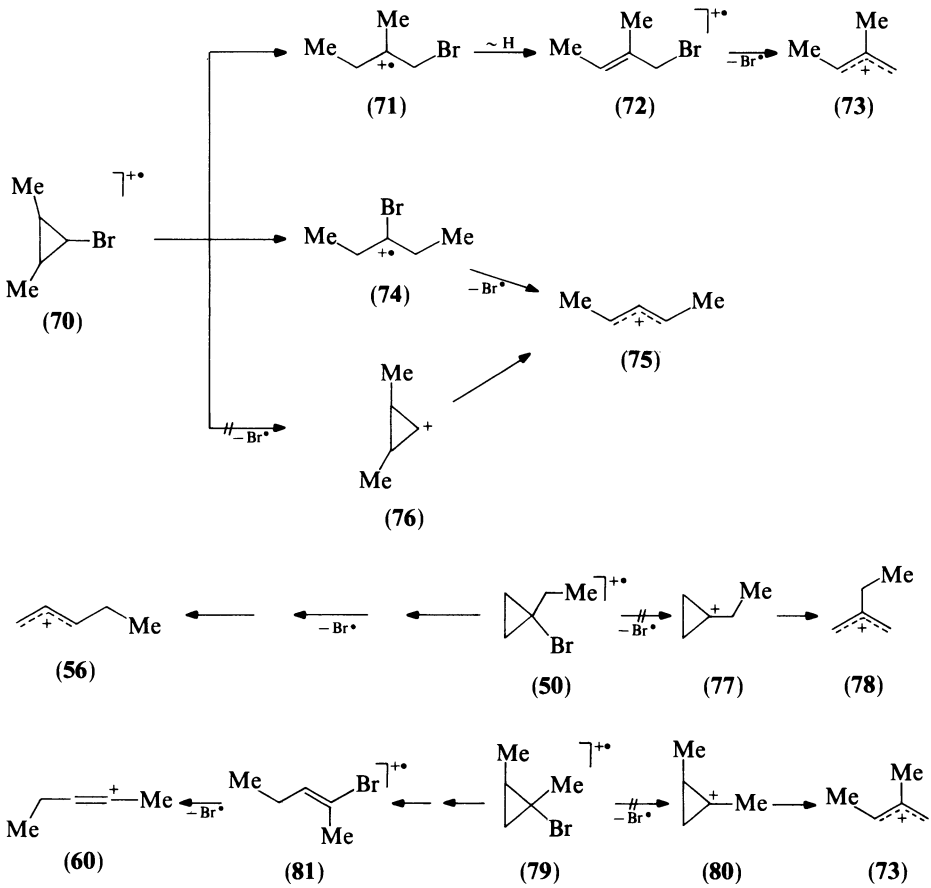
The so-formed intermediates undergo various rearrangements (including hydrogen and alkyl shifts) prior to the expulsion of Br$^{\cdot}$. Direct elimination of Br$^{\cdot}$ from intact



SCHEME 7



SCHEME 8

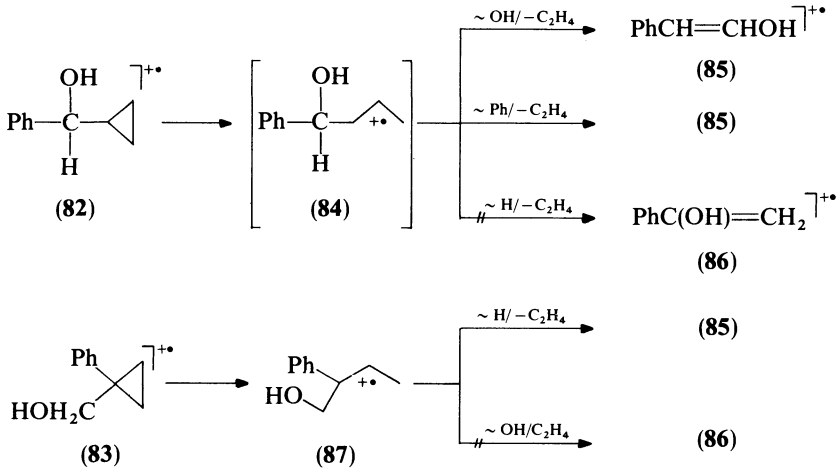


SCHEME 9

cyclopropane-like structures, followed by isomerization of the intermediate cyclopropyl cations, cannot compete energetically with the multistep sequences outlined in Schemes 7–9.

The structures and the formation of $[C_8H_8O]^{+\cdot}$ ions generated from ionized phenylcyclopropylcarbinol (**82**) and 1-phenyl-1-(hydroxymethyl) cyclopropane (**83**) formed by electron impact have been investigated by Nibbering *et al.*[38] using kinetic energy release measurements, by determination of ionization and appearance energies and by collisional activation studies. In perfect agreement with the original proposal of Sisido *et al.*[39] they found that the non-decomposing $C_8H_8O^{+\cdot}$ ions, generated from either **82** and **83**, have exclusively the structure of the enol ion of phenylacetaldehyde (**85**), although this ion is less stable than the enol ion of acetophenone (**86**) by as much as 10.8 kcal mol^{-1}. Nibbering *et al.* interpret the formation of **85** from **82** as indicating that **82** does not simply undergo **82** → **84** ring opening (Scheme 10), followed by further reactions. If such were the case, ion **86** but not **85** would have been formed for it is well known that hydrogen migration (**84** → **86**) is much faster than phenyl or hydroxyl migration. Therefore, they

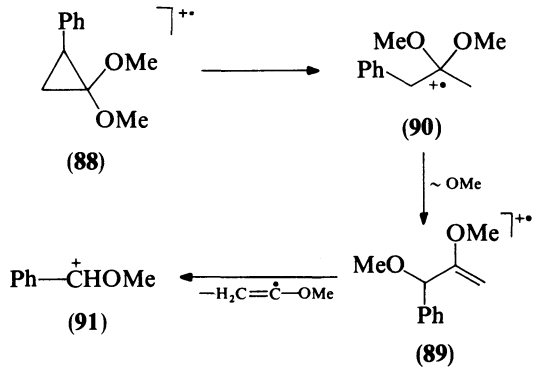
suggest that **84** is not formed as a discrete intermediate but that the cyclopropane ring of **82** is opened by an intramolecular attack of either the phenyl ring or the hydroxyl group on the C(1)–C(2) bond with a simultaneous expulsion of C_2H_4 and migration of the attacking group to C(1), thereby eventually generating **85**. Investigation of D-labelled compounds[39] showed that the ratio of Ph versus OH migration is approximately 2. Such a view is corroborated by the exclusive formation of **85** from the molecular ion of **83** by loss of C_2H_4. In this case the cyclopropane ring can be opened easily by a benzylic cleavage to give an intermediate **87** in which not only one of the methylene hydrogen atoms (**87** → **85**) but also the hydroxyl group might migrate (**87** → **86**) to the benzylic carbon atom prior to or during the expulsion of C_2H_4. Hydroxyl migration can be excluded by the fact that the resulting $C_8H_8O^{+\cdot}$ is not **86** but pure **85**. Formation of **86** (which can easily be distinguished from **85** by inspection of their CA mass spectra) is not observed, thus ruling out OH migration.



SCHEME 10

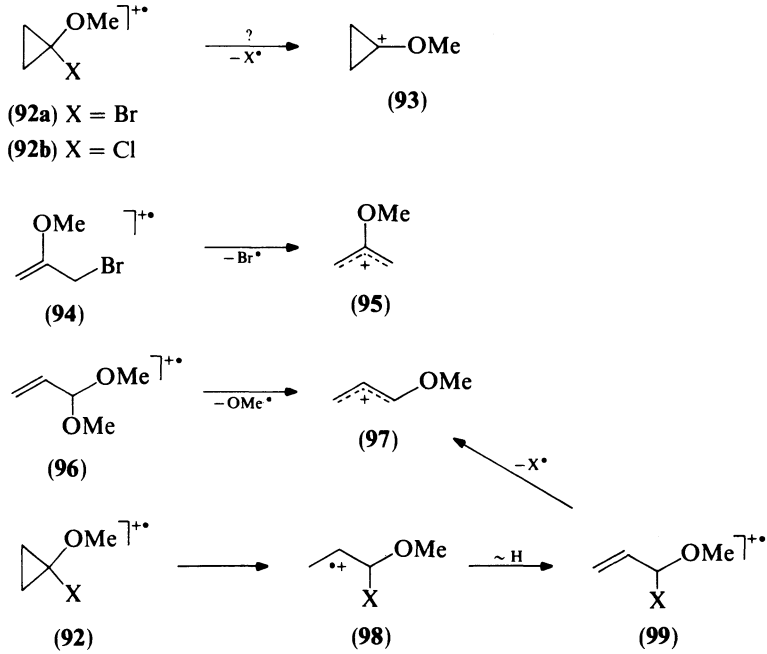
Methoxy migration in a ring-opened cyclopropane is of decisive importance for the gas phase chemistry of ionized 1,1-dimethoxy-2-phenylcyclopropane (**88**)[40]. The major fragment in the 70 eV electron impact mass spectrum of **88** appears at *m/z* 121; the same fragment is also the major ion in the mass spectrum of **89** (loss of CH_2=$\dot{C}$–OMe). Collisional activation proves the structural identity of both ions with *m/z* 121 and reveals that the most likely structure is that of **91**. An obvious explanation is that the ring opening of **88** to **90** is accompanied (or followed) by 1, 2-migration of the methoxyl group (Scheme 11), which via **89** gives rise to the formation of **91**.

The question as to whether dissociative ionization of **92** (loss of X$^{\cdot}$) does result in the generation of the long-sought 1-methoxycyclopropyl cation (**93**) is of interest in theoretical[41] and physical organic chemistry [42,43]. By using ICR it was shown [42] that the $[M–Br]^+$ ions from **92a** and from **94** exhibit very different ion/molecule reactivities toward various proton and methyl cation acceptors. Consequently, it was suggested that this different reactivity pattern may be indicative of the presence of two distinct ions, one of which was believed to be the 1-methoxycyclopropyl cation (**93**) and the other the 2-methoxyallyl cation (**95**), the latter being formed from **94**. Species such as the 1-methoxyallyl cation (**97**), which can be generated conveniently from **96**, were not taken



SCHEME 11

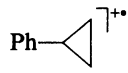
into consideration. In the interpretation that ionized **92** may dissociate directly to the ring-intact fragment ion **93** it was tacitly assumed that ring-opening by cleavage of the C(1)–C(2) or the C(1)–C(3) bond cannot compete effectively, or is at most of minor importance, with direct cleavage of the C(1)–X bond. While there are many precedences[6, 13, 44] that cyclopropane derivatives may indeed remain cyclic upon electron impact ionization, the preceding discussion indicates, however, that it is more likely that 'reactive' ions dissociate preferentially to form ring-opened structures. In fact, a detailed structural analysis[43] of the species generated from **92**, **94** and **96**, respectively, clearly indicated that



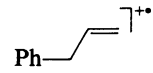
SCHEME 12

both **92** and **96** give rise to the formation of **97**, whereas **94** fragments to **95**. There is no evidence for the formation of **93** from either precursor used. Whereas dissociation of **94** and **96** are straightforward, loss of X$^{\cdot}$ from **92** requires a multistep sequence commencing with ring-opening (**92** → **98**) followed by hydrogen migration (**98** → **99**) and eventual loss of X$^{\cdot}$ (Scheme 12).

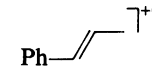
Ring-opening and isomerizations are also involved in the chemistry of ionized phenylcyclopropane (**100**)[45]. Whereas at times as short as 10^{-11} s the field ionization spectra of **100** and **101** are distinctly different, indicating that these ions maintain unique structures as is also the case in photoionization matrix isolation experiments[46]. At longer lifetime ($t = 10^{-6}$ s) equilibration has taken place in which **100** rearranged to **101**. It is noteworthy, that ionized β-methylstyrene (**102**) does not participate in this rearrangement at least when non-decomposing $C_9H_{10}^{+\cdot}$ species are concerned[48]. In contrast, energetic measurements[47] suggest that **100, 101, 102** and some other $C_9H_{10}^{+\cdot}$ isomers do rearrange prior to H· loss to a common (yet unknown) structure.



(**100**)



(**101**)

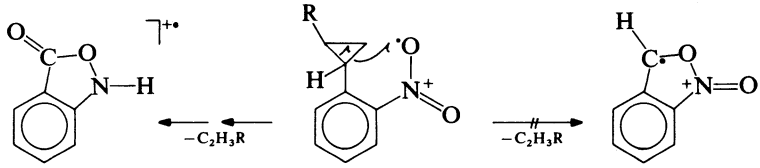


(**102**)

Isomerization reactions of ionized cyclopropane derivatives indeed seem to be ubiquitous and many further examples are reported in Refs 49 and 50. However, a careful examination of randomly selected papers[51, 52] indicates that the generality of these processes is not likely to be recognized, because the results and strange interpretations presented in these articles could easily be accounted for by mechanisms described in this chapter instead of the ones originally proposed[51,52].

B. Anchimercally Assisted Ring-opening of Substituted Cyclopropane Ions

The reaction sequence **82** → → **85** (Scheme 10) may already be viewed as a prototype for ring-opening of cyclopropanes induced by neighbouring group participation. A more striking example may be found in the gas phase chemistry of ionized *ortho*-substituted cyclopropyl nitrobenzenes (**103**). The 70 eV electron impact mass spectrum of **103** is dominated by an intense signal (base peak) at *m/z* 135 ($C_7H_5NO_2$) which is due to the loss of C_2H_3R from the molecular ion of **103**[53, 54], and investigation of various D-labelled isotopomers of **103** reveals that the β-methylene groups of the cyclopropane ring are exclusively involved in the expulsion of ethylene[55]. The low intensity of $C_7H_5NO_2^{+\cdot}$ ions in the mass spectra of the *meta* and *para* isomers of **103a** clearly points to the operation of an *ortho* effect[56], and to account for the specific role of the *ortho* NO_2 substituent in the course of the reaction Chochna *et al.*[54] have suggested that ion **104** may be formed according to Scheme 13. That ion **104** is *not* generated from **103**, and therefore the suggested one-step process **103** → **104** is not operative, could easily be demonstrated in a collisional activation experiment. It was shown[57] that loss of C_2H_3R (R=H, Me) exclusively leads to the formation of ionized 2,1-benzisoxazolin-3-one (**105**), which in an earlier study[58] had already been shown to be the only product formed in the dissociative intramolecular redox reactions of various nitrobenzene derivatives. Although the detailed mechanism for the dissociative rearrangement **103** → **105** has to be settled, the results reported in Ref. 57 establish not only the operation of another interesting intramolecular redox reaction[59] but are clearly indicative for an anchimerically assisted ring-opening of the cyclopropane ring.



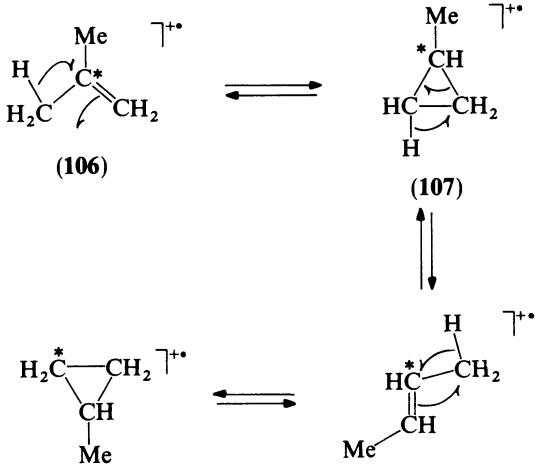
(105) (103a) R = H (104)
(103b) R = Me

SCHEME 13

Neighbouring group participation governs also the mass spectral behaviour of isomeric cyclopropyl-substituted pyridine ketones[60]. While the mass spectra of the respective *meta* and *para* isomers do not exhibit any signals originating from specific interactions of the two ring systems, in the spectra of the *ortho* compounds signals are found (for example loss of C_2H_4 from $M^{+\cdot}$) which are best explained by interaction between the nitrogen and the cyclopropane ring. However, the authors[60] do not provide any experimental or theoretical evidence to substantiate their rather speculative conclusions concerning the nature of this interaction.

IV. IONIC CYCLOPROPANES AS INTERMEDIATES OR STABLE PRODUCTS IN REARRANGEMENT/DISSOCIATION PROCESSES

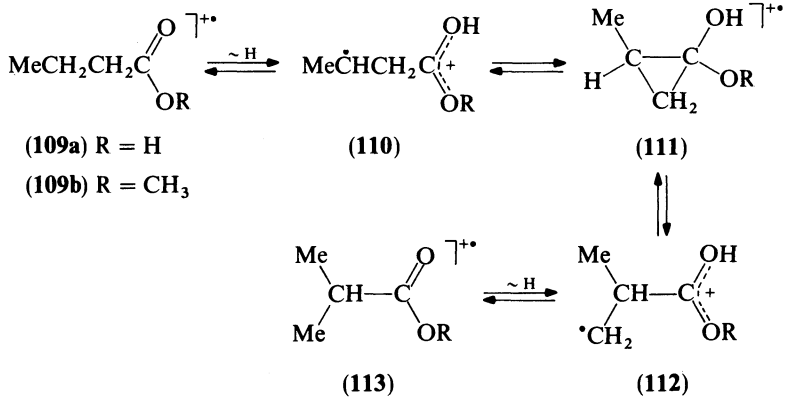
The fact that the decomposition of ionized methylpropene (**106**) at longer lifetimes is preceded not only by hydrogen randomization but also by participation of the C(2) carbon atom (indicated with an asterisk in Scheme 14) in the expulsion of ethylene has been explained[61,62] by invoking the intermediate existence of methylcyclopropane (**107**) and 2-butene (**108**) (Scheme 14). This is in line with the finding that direct ionization of neutral methylcyclopropane gives **107** which is known to undergo ethylene loss[63]. The isomerization sequence described in Scheme 14 can be viewed as a further example for a mass spectrometric dyotropic rearrangement[64].



(106) (107)

(107a) SCHEME 14 (108)

Cyclopropane-like intermediates seem also to be involved in the loss of ethylene from ionized *n*-butanoic acid (**109a**)[65]. By using D- and ^{13}C-labelled isotopomers of **109a** it was demonstrated that at a lifetime $t > 10^{-6}$ s loss of ethylene does not only involve the C_β and C_γ (via a McLafferty rearrangement) and C_β and C_α (via the formation of cyclobutane-like intermediates[66]), but most interestingly also the γ- and α-carbon atoms. This has been explained by assuming that at longer lifetimes **109** undergoes reversible isomerization involving **111a** (R=H) as the crucial intermediate which links the common features of the gas phase ion chemistry[65] of *n*- and *i*-butanoic acids (Scheme 15). It should be noted, however, that recent MNDO calculations[67] have indicated that **111a** (R=H) is not a stable species but rearranges spontaneously via ring-opening to either **110a** (R=H) or **112a** (R=Me).



(**109a**) R = H (**110**) (**111**)

(**109b**) R = CH_3

(**113**) (**112**)

SCHEME 15

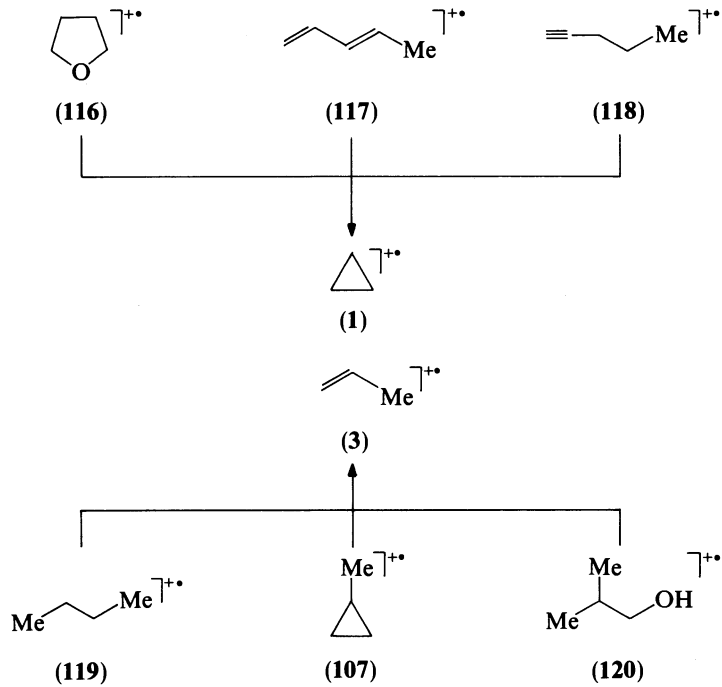
Similarly, a detailed analysis of the field ionization kinetic data together with D-labelling has indicated that ethylene loss from ionized methyl isobutyrate (**113b**; R=Me) is a relatively slow process[68], induces by a so-called hidden hydrogen rearrangement[36]. The sequence shown in Scheme 15 has been used to rationalize the interconversion of **109b**, **111b** and **113b**, respectively, and the experimental data indicate that a complete equilibrium between these species is achieved after 7×10^{-6} s.

The formation of cyclopropane derivatives has also been invoked to explain the mass spectrometric behaviour of 4-phenyl-substituted 2,3-dihydrofurans (**114**)[69]. It was found that the main fragmentation peaks in the mass spectra of **114** and **115** (R^1, R^3, R^4 = H,Me, R^2 = Ph) can be interpreted in terms of an equilibrium (valence isomerization) between the parent ions (Scheme 16).

(**114**) (**115**)

SCHEME 16

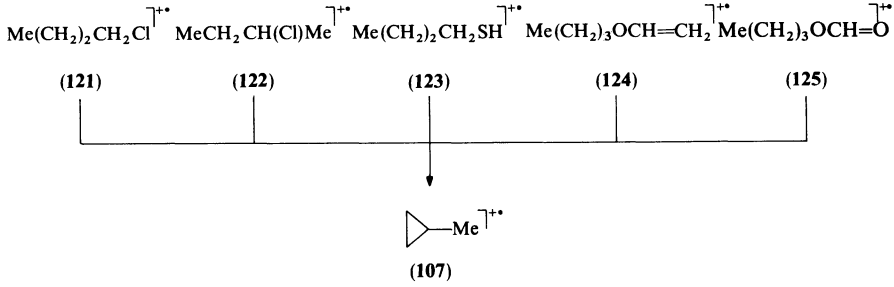
The formation of cyclic structures not only as transients but also as stable product ions is conceivable for quite a number of gas phase reactions. However, unambiguous assignments of the structures could in most cases be obtained only by combining various experimental techniques. Even the simplest process, i. e. the formation of $C_3H_6^{+\cdot}$ product ions from various precursors, has been debated controversially for many years, and only recently it was shown [10,11,70] that ionized cyclopropane (**1**) is produced from the cation radicals of tetrahydrofuran (**116**), penta-1,3-diene (**117**) and pent-1-yne (**118**), whereas ionized butane (**119**), methylcyclopropane (**107**) and 2-methylpropan-1-ol (**120**) yield ionized propene (**3**) as the sole product upon dissociation (Scheme 17).



SCHEME 17

Despite its high heat of formation ($\Delta H_f^0 = 224$ kcal mol^{-1})[71] the next higher homologue of **1**, i. e. the cation radical of methylcyclopropane (**107**) appears to be formed as a substantial fraction of the $C_4H_8^{+\cdot}$ product ions generated from 1- and 2-chlorobutane (**121, 122**), 1-butanethiol (**123**), *n*-butyl vinyl ether (**124**) and *n*-butyl formate (**125**), as evidenced by labelling studies[72], kinetic energy release measurements[73] and the analysis of collision induced dissociations[74] (Scheme 18).

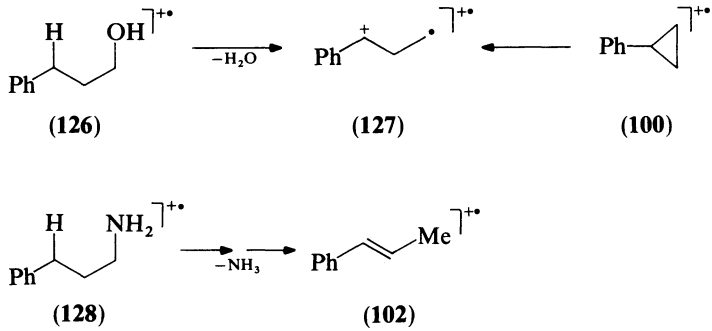
A most detailed study on the isomerization and dissociation characteristics of small C_5H_{12} molecular ions, employing appearance energy measurements, labelling studies and the analysis of kinetic energy release data was performed by Holmes *et al.*[75]. For methylbutane molecular ions of low internal energy content it was found that loss of C_2H_6 yielded ionized propene (**3**); loss of CH_4 proceeded at an energy greater than that calculated for the production of ionized but-2-ene (**108**), 2-methylpropene (**106**), but-1-



SCHEME 18

ene, or methylcyclopropane (**107**), and the labelling experiments indicate that different daughter ions are indeed being generated via competing mechanistic pathways.

The previously[76] reported 1,3-water loss from ionized 3-phenylpropanol (**126**) leads initially to **127**. This is in contrast to the formation of ionized β-methylstyrene (**102**) by 1,3-ammonia elimination from 3-phenylpropylamine (**128**)[77]. As **127** may also be generated by simple ring opening of cyclopropylbenzene (**100**)[45] it is not surprising that the CA mass spectra of $C_9H_{10}^{+\cdot}$ ions generated from either **126** or **100** are indistinguishable (Scheme 19).

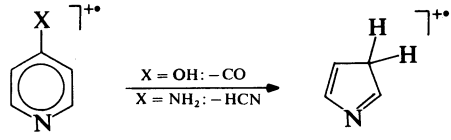


SCHEME 19

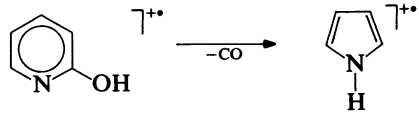
No cyclopropane-like product ions, i.e. cyclopropyl cyanide ion (**7**), were generated from various pyridine precursors. By using collisional activation it was shown that 4-hydroxy- or 4-aminopyridines (**129**) dissociate via loss of CO or HCN, respectively, to form 3*H*-pyrrole (**130**), whereas CO loss from ionized 2-hydroxypyridine (**131**) gives rise to the formation of 1*H*-pyrrole (**10**). In other cases, mixtures of 2*H*- and either 1*H*- or 3*H*-pyrroles are generated, depending on the nature of the precursor[78,79]. (Scheme 20).

Quite unexpected was the recently reported[80] ring-closure reaction associated with $Cl^{\cdot}$ loss from the molecular ion of α-methyl-β-chloropropionitrile (**132**), which yields 30% $C_4H_6N^+$ ions which have the structure of *N*-protonated cyclopropyl cyanide (**134**). The intermediacy of **133** was suggested (Scheme 21).

Similarly surprising is the finding of Stolze and Budzikiewicz[81] that the molecular ions of the tetrahydrofuran derivatives (**135**) dissociate to *O*-protonated cyclopropyl carboxaldehyde (**136**), which is also formed directly from **137** (Scheme 22).

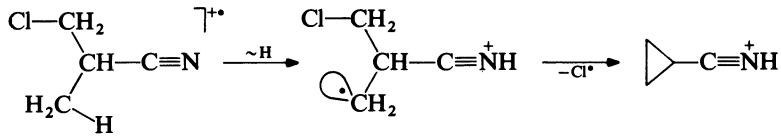


(129) X = OH, NH_2 (130)



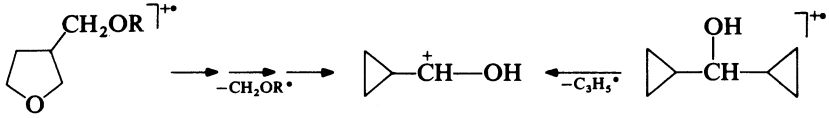
(131)· (10)

SCHEME 20



(132) (133) (134)

SCHEME 21



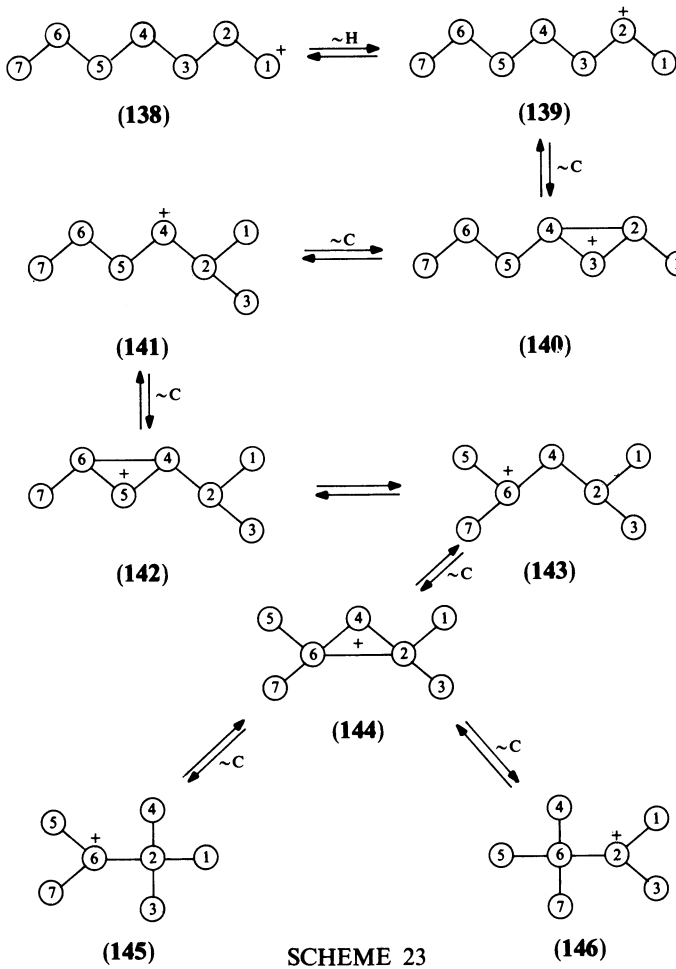
(135) (136) (137)

R = H, Ac

SCHEME 22

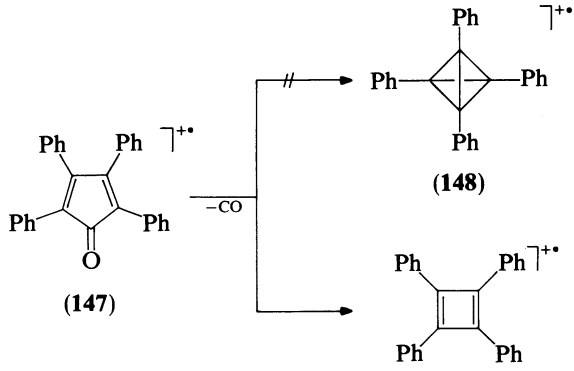
Ring-protonated alkylcyclopropanes, well-known in solution[82], were suggested to explain the most unusual behaviour of heptyl ions. Extensive ^{13}C- and D-labelling[83] as well as a computer simulation[84] and the analysis of CA data[85] indicate that the major fragmentation reactions of $C_7H_{15}^+$ ions, generated via loss of I· from 1-heptyl iodide, are preceded by extensive skeletal reorganization which via cyclopropane-like structures (**140**, **142**, **144**) eventually isomerize to tertiary carbocations (**145** and **146**, Scheme 23 where only the carbon skeleton is shown). The latter serve as actual precursors for the loss of C_3H_6.

In contrast to earlier interpretations[86] gas phase decarbonylation of ionized 2,3,4,5-tetraphenyl-2,4-cyclopentadienone (**147**) does not result in the formation of an ionized tetraphenyl-substituted tetrahedrane (**148**), but yields exclusively the isomeric cyclobutadiene derivative (**149**)[87] (Scheme 24).



(138) (139) (141) (140) (142) (143) (144) (145) (146)

SCHEME 23



(147) (148) (149)

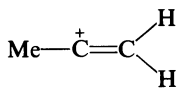
SCHEME 24

V. ISOMERIZATION OF CLOSED-SHELL CYCLOPROPANE CATIONS

The stereospecific ring-opening reactions of cyclopropyl derivatives have played a key role in establishing selection rules for pericyclic processes[88]. Extensive and conclusive evidence has been presented in support of DePuy's initial postulation[89] that disrotatory ring-opening and C–X bond heterolysis are synchronous processes, and all kinetic[90], stereochemical[91] and theoretical[92] findings lend credence to the DePuy–Hoffmann–Woodward rule[89, 93]: 'Substituents on the same side of the 3-membered ring as the leaving group rotate towards one another, whereas those on the other side rotate apart.'

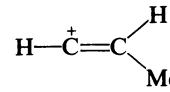
Before presenting evidence for the occurrence of exactly the same type of reactions in the gas phase, the chemistry of gaseous $C_3H_5^+$ ions which has been the subject of both experimental[94] and theoretical[92c,d, 95] studies should be discussed briefly. In the present context it is of interest to state that there is experimental evidence for the existence of both allyl (**150**) and 2-propenyl cations (**151**), which do not interconvert. There is no evidence for the formation of either cyclopropyl cation (**152**) or the 1-propenyl cation (**153**). The former, if generated at all, rearranges to the allyl cation, whereas the latter undergoes isomerization to **151**.

(**150**)



(**151**)

(**152**)



(**153**)

Of particular theoretical[96] and experimental[97] interest is the detailed pathway by which isomeric $C_3H_5CO^+$ ions undergo unimolecular CO loss in the gas phase. In agreement with the experimental results, MNDO calculations indicate that CO loss from CH_2=CH–CH_2CO^+ (**154**), *c*-$C_3H_5CO^+$ (**155**) and MeCH=$\overset{+}{C}$HCO (**156**) gives exclusively the allyl cation (**150**), whereas CH_2=C(Me)CO^+ (**157**) dissociates specifically to **151**. Most interesting is the result that, whereas CO loss from **154** and **157** are continuously endothermic reactions, the analogous dissociations of **155** and **156** follow more complicated pathways, which are depicted as potential diagrams (MERP) in Figures 3 and 4. For **155**, the energetically most favoured reaction involves isomerization to **154** via the intermediates α-oxo and β-oxocyclobutyl cations **159** and **160**, respectively. This reaction sequence is 10 kcal mol^{-1} *lower* in energy than direct CO loss from **155** coupled with isomerization of the complex of the incipient cyclopropyl cation/neutral CO (**158**) to separated allyl cation (**150**) and CO. For **156** it is predicted that this ion undergoes isomerization to **154** via **155** prior to CO loss. The alternative reaction, i.e. direct CO elimination giving rise to 1-propenyl cation (**153**) or direct isomerization to **154** via 1,3-hydrogen migration were found to be 35 and 43 kcal mol^{-1} higher in energy than the process **156** → **155** (Figure 4).

Andrist *et al.*[98] employed chemical ionization mass spectrometry to examine the ion/molecule chemistry resulting from the gas phase protonation of the isomeric 2,3-dimethylcyclopropyl methyl ethers (**164–166**)[98a,b] in a search for gas phase electrocyclic processes. Chemical ionization of each isomer with H_2, CH_4 and NH_3 produced in each case oxygen protonation, as major fragmentation pathway, followed by loss of MeOH. Their results are entirely consistent with expectations stemming from the known solvolysis rates of the isomeric 2,3-dimethylcyclopropyl tosylates[90]. With all reagent gases for the isomer **166**, where it is predicted by the DePuy rule[89, 93] that both methyl groups rotate apart in the transition state, a larger proportion of its total ion current is due to the $[MH–MeOH]^+$ ion than for the isomer **165** and even less for **164**. In spite of the fact that the ion structures of the resulting $[MH–MeOH]^+$ species (**75**, **167**, **168**) have not yet been

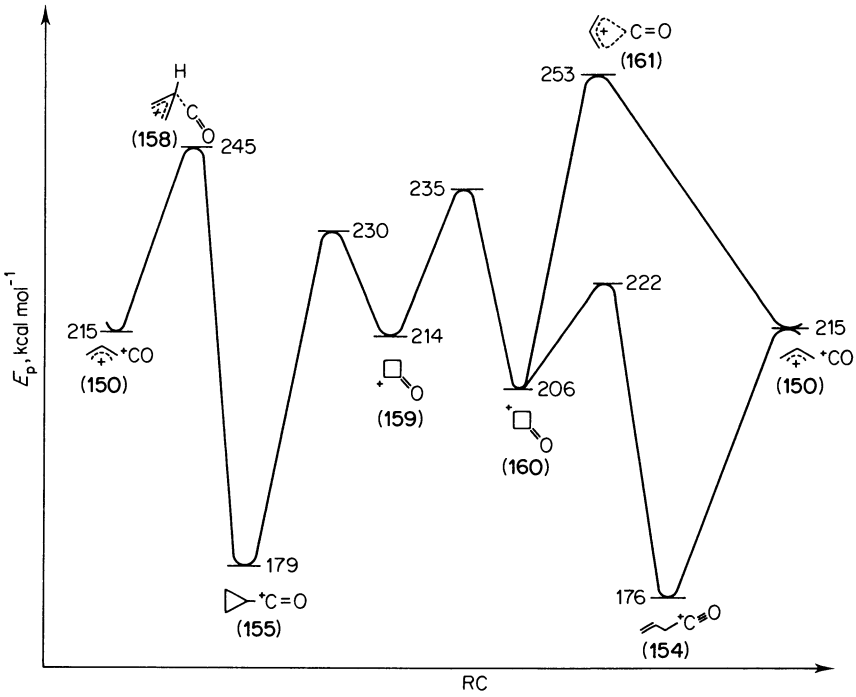


FIGURE 3. MNDO-MERP for isomerization of and CO loss from *c*-$C_3H_5\overset{+}{C}O$ (**155**).

determined explicitly, the results (Scheme 25, intensities are given as % total ion current, TIC) are clearly rationalized as a gas phase electrocyclic reaction occurring in the preferred manner as prescribed by orbital symmetry conservation.

Similar studies on the gas phase chemistry of cyclopropyl thioethers were reported by Chizhov *et al.*[99]. The conclusions drawn in the investigation were, however, hampered by the fact that protonation seems to occur competitively at both the cyclopropane ring, the sulphur atom and the aryl ring.

Protonation of the cyclopropane ring can easily be achieved in the gas phase, and the collisional activation mass spectra of the so-obtained $C_3H_7^+$ ions were found[100] to be perfectly identical with the one obtained from protonation of propene. This has been interpreted as evidence that the isomerization *c*-$C_3H_7^+ \rightarrow$ *s*-$C_3H_7^+$ is completed in $t < 10^{-5}$ s.

The quite complicated pattern resulting from protonation of the C_4H_8 isomers, *cis*- and *trans*-2-butene, 1-butene and methylcyclopropane from various gas phase proton donors (such as $MeCNH^+$, $MeCHOH^+$, AsH_4^+, H_3S^+ and H_3O^+) were studied in great detail by Ausloos and Lias[101]. They did not only determine the structures of the resulting $C_4H_9^+$ ions (*s*-butyl or *t*-butyl cations) but also provided a convincing mechanistic rationale for the energetics of the protonation/isomerization steps. Of particular interest was their finding that the probability of rearrangement in the complex $[M \cdots H \cdots C_4H_8]^+$ is greater, the greater the dipole moment of the M species; this is due to the fact that a larger dipole moment is associated with a deeper well depth for the ion/molecule complex, and hence with a lower energy for the 'transition state complex'. Their model can also

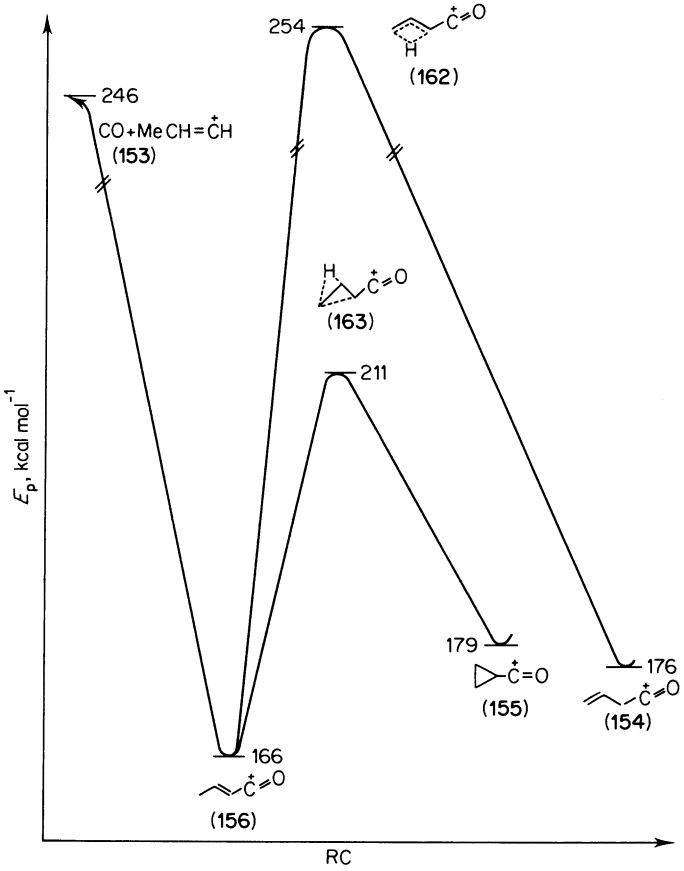
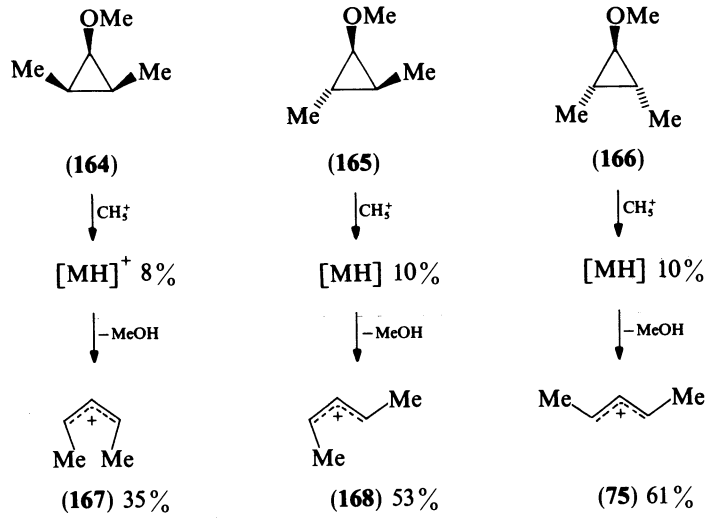


FIGURE 4. MNDO-MERP for isomerization of **156** and direct CO loss **156** → **153**

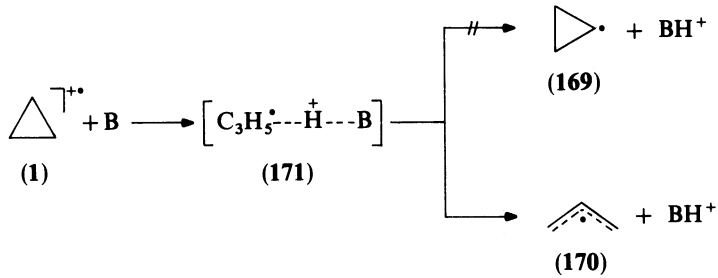
successfully be used to explain various literature results on structure retention or ring-opening in protonated cyclopropane rings in the gas phase. It should be mentioned that, in contrast to solution studies, there is no clear-cut evidence for the existence of a discrete protonated methylcyclopropane ion in the gas phase[102]. This is consistent with the above-mentioned result on protonation of the lower homologue, i.e. *c*-C_3H_6[100], although there are some claims in the literature[103] that *c*-$C_3H_7^+$ might be a viable species in the gas phase, in equilibrium with *s*-$C_3H_7^+$.

c-C_3H_6 can act as a proton acceptor towards Brønsted acids MH^+ thereby generating $C_3H_7^+$ ions, but the cation radical *c*-$C_3H_6^{+\cdot}$ can also transfer a proton to suitable bases B, thus forming BH^+ and $C_3H_5^+$: The controversies over the energetics of the latter reaction have been settled recently[15], and it is now accepted that the apparent proton affinity of the $C_3H_5^\cdot$ conjugate base —generated when a proton is transferred from cold *c*-$C_3H_6^{+\cdot}$—is 179 kcal mol^{-1}, which is lower than that which would be predicted for the cyclopropyl radical (**169**) (187–192 kcal mol^{-1}). Thus it was suggested that the anomalously low value



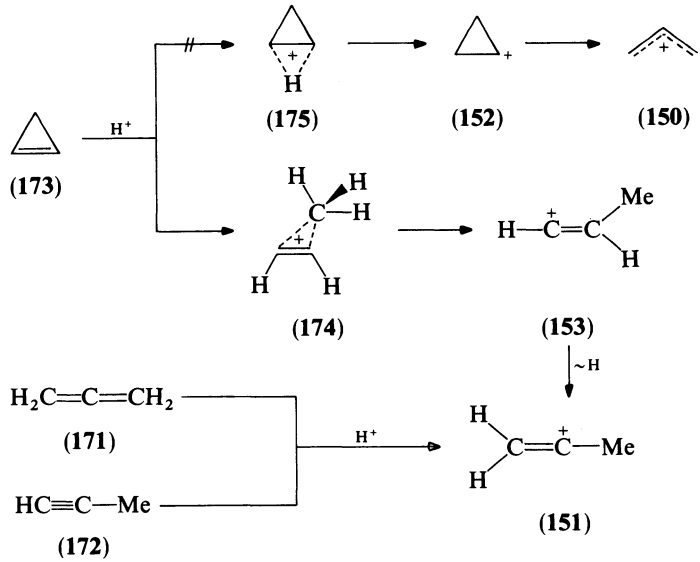
SCHEME 25

observed for the proton affinity indicates ring-opening of the incipient cyclopropyl radical (**171**) to the allyl radical (**170**) in the course of the proton transfer reaction (Scheme 26).



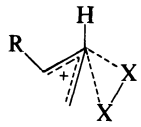
SCHEME 26

Similarly revealing is the solution of a long-standing problem offered by Köhler and Lischka[92d] for the protonation of C_3H_4 species. Whereas experimentally determined and theoretically evaluated proton affinities of allene (**171**) and propyne (**172**) could be reproduced within experimental accuracy, the calculated proton affinity of cyclopropene (**173**) deviates significantly from the experimental value if, as had been done in the literature, the cyclopropyl cation (**152**) is assumed to be generated initially as the protonated species. In order to resolve this discrepancy Köhler and Lischka[92d] investigated in great detail the $C_3H_5^+$ potential energy surface and searched for reasonable alternatives. As a solution of the problem they suggested that protonated cyclopropene (**175**) had not been formed at all, but that an asymmetrically, corner-protonated species (**174**) was first generated, and then collapsed via the primary vinyl cation (**153**) to the 2-propenyl cation (**151**). The latter is also generated directly when **171** and **172** are being protonated (Scheme 27). Using this model Köhler and Lischka obtain a proton affinity for **173** of 199.7 kcal mol^{-1} which is in reasonable agreement with the experimental value of 194 ± 3 kcal mol^{-1} [94d].



SCHEME 27

In the discussion of the gas phase chemistry of $c\text{-}C_3H_5CO^+$ ion (**155**) it was stated that direct CO loss via a partially ring-opened cyclopropyl cation interacting with CO as a solvating species, i.e. species **158** (Figure 3) is not likely to occur. There are, however, quite a number of systems which are best described by involving transition states of the general structure **176**. These structures can be viewed as a partially ring-opened cyclopropyl cation which is 'solvated' by either a σ-ligand (for example H_2 in the reaction $C_3H_7^+ \rightarrow C_3H_5^+ + H_2$) or a π-ligand (i.e. C_2H_4 in the processes $C_5H_9^+ \rightarrow C_3H_5^+ + C_2H_4$ and $C_6H_{11}^+ \rightarrow C_4H_7^+ + C_2H_4$)[104]. Both experimental and theoretical work[104–107] suggest that the principal features of the unimolecular chemistry of many carbocations can be conveniently described by invoking intermediates which eventually dissociate via **176** to allyl-type product ions.



(176)

R	X	Reaction	Ref.
H	H	$C_3H_7^+ \rightarrow C_3H_5^+ + H_2$	105
H	CH_2	$C_5H_9^+ \rightarrow C_3H_5^+ + C_2H_4$	106
Me	CH_2	$C_6H_{11}^+ \rightarrow C_4H_7^+ + C_2H_4$	107

VI. GASEOUS CYCLOPROPYL ANIONS

There are quite a number of theoretical papers[88, 93, 95a, 108] on the relationship between $C_3H_5^-$ anions having the allyl (**177**), vinyl (**178–180**) and cyclopropyl structures (**181**) (Figure 5).

Under normal circumstances it would appear that both the cyclic and the allylic structures of $C_3H_5^-$ should exist with little probability of interconversion due to the high

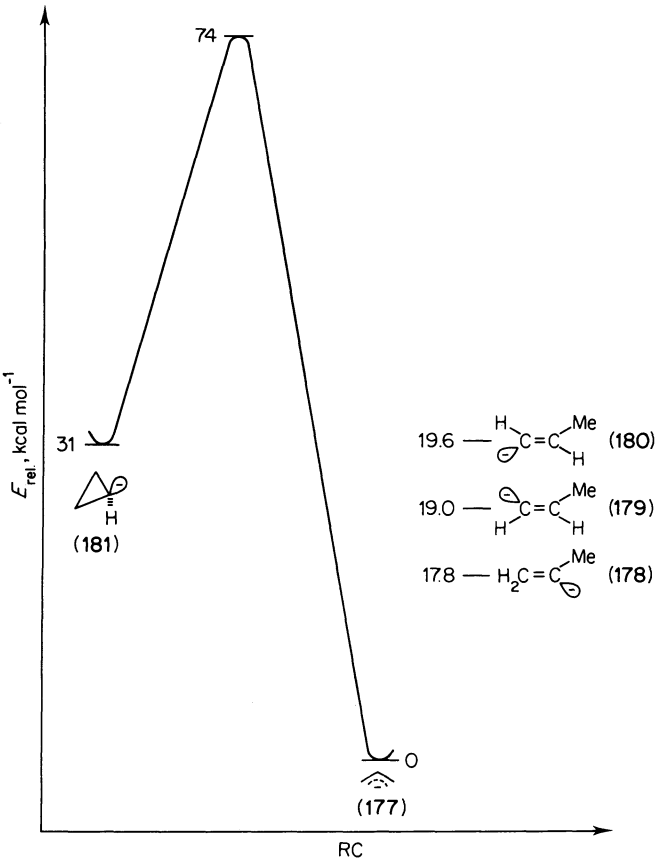
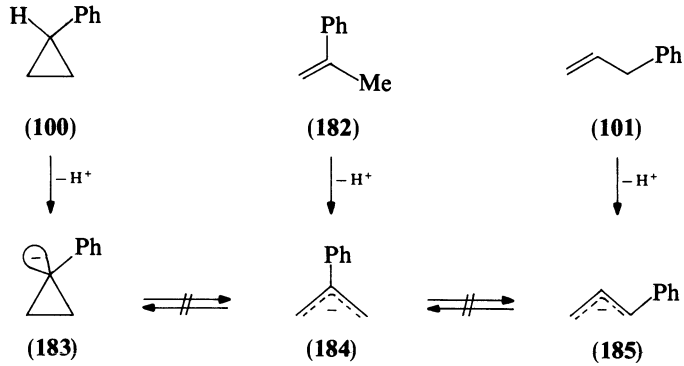


FIGURE 5. Relative thermochemical data for $C_3H_5^-$ isomers[95a, 108a, b, 109c].

barrier separating **177** and **181**. However, all experimental efforts to generate **181** failed[109] (see, however, Section VII and Ref. 147). The only stable $C_3H_5^-$ species generated in the gas phase is so far the allyl anion (**177**). For long-lived (**177**) it could be demonstrated by studying labelled species, that the allyl anion have little, if any, tendency to undergo hydrogen scrambling processes. This means in effect that the activation energy available to these ions can neither exceed the exothermicity of the reaction in which they are formed ($O^{-\bullet} + MeCH = CH_2 \rightarrow OH^- + C_3H_5^-$) nor the electron affinity (EA) of the allyl radical. The latter is as much as 12.7 kcal mol^{-1} [109c].

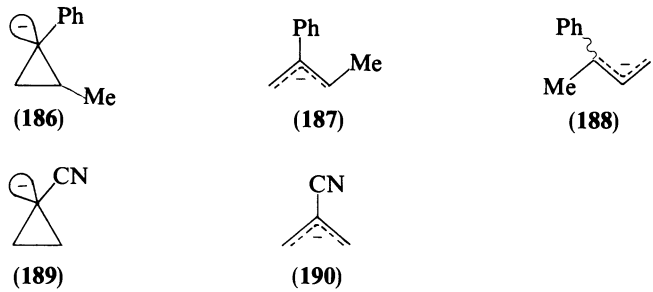
In contrast, quite a number of substituted $C_3H_4X^-$ isomers were generated in the gas phase and characterized by their distinct pattern of ion/molecule reactions. For example, proton abstraction by NH_2^- from phenylcyclopropane (**100**), 2-phenylpropene (**182**) and 3-phenyl-1-propene (**101**) gives exclusively *m/z* 117 product ions. These $C_9H_9^-$ ions **183–185** are readily distinguishable by their differing reactions with D_2O, O_2 and N_2O[110], thus demonstrating that interconversion must be impeded by relatively high barriers (Scheme 28).



SCHEME 28

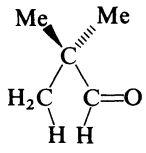
The specifically generated 2-methyl-1-phenylcyclopropyl (**186**) and 1-methyl-2-phenylallyl anions (**187**) were also shown[110] to exist as stable, non-interconverting isomers. However, in the presence of H_2O **187** is converted to the 1-methyl-1-phenylallyl anion (**188**) by reversible proton addition and re-abstraction.

Similarly, it was convincingly demonstrated by Dawson and Nibbering[111] that the species **189** and **190** are distinct stable carbanions both in the gas phase as well as in solution.

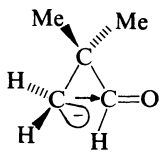


A detailed study on homoconjugation versus charge dipole interaction effects which may account for stabilities of some primary gaseous carbanions was performed by the same research group[112]. 2,2-Dimethylpropanal (**191**) is easily deprotonated in the gas phase. and its gas phase acidity was determined to be between that of H_2O (391 kcal mol^{-1}) and MeOH (379 kcal mol^{-1})[113]. With D_2O eight out of the nine hydrogen atoms in the $C_5H_9O^-$ ion could be exchanged. The unexpectedly high gas phase acidity observed for **191** indicates that the stabilization of the $(M–H)^-$ ions by as much as 37 kcal mol^{-1} is to a large part due to a simple interaction between the charge in an sp^3 orbital and the dipole moment of the functional group, as indicated in structure **192**. By using the formula $E = -q\mu \cdot \cos\theta/r^2$ and favourable conformations, it is roughly estimated that 21 kcal mol^{-1} stabilization energy will be available to the$[M–H]^-$ ions of **191**. Some further stabilization energy may come from polarizability effects and from hyperconjugative contributions from the polar group, but this is difficult to quantify. There remains the question of whether or not homoconjugative effects also contribute to the stabilization of the anion. In theory, after rehybridization, homoconjugation could eventually lead to ring closure (**193**) and isomerization of the ion to a cyclopropoxide anion (**193a**). However, the H/D

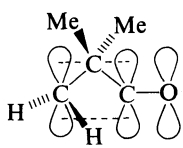
exchange experiments mentioned previously indicate that if such an isomerization occurs at all, it must be very slow.



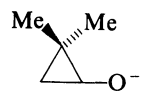
(191)



(192)

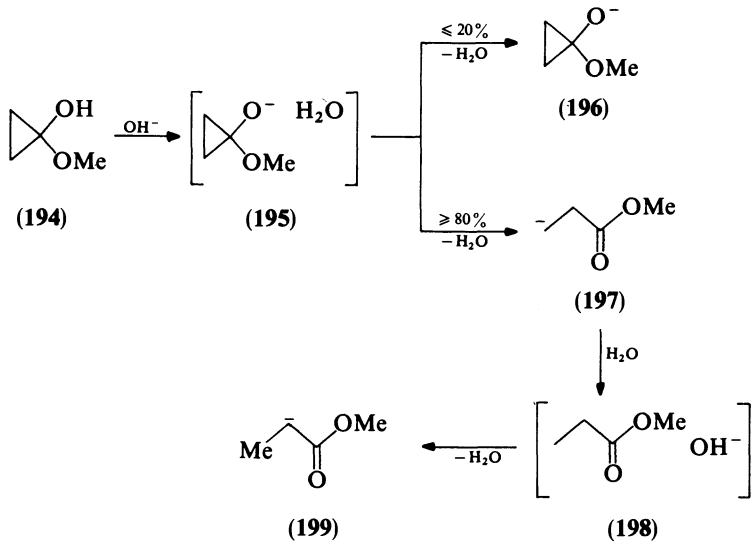


(193)



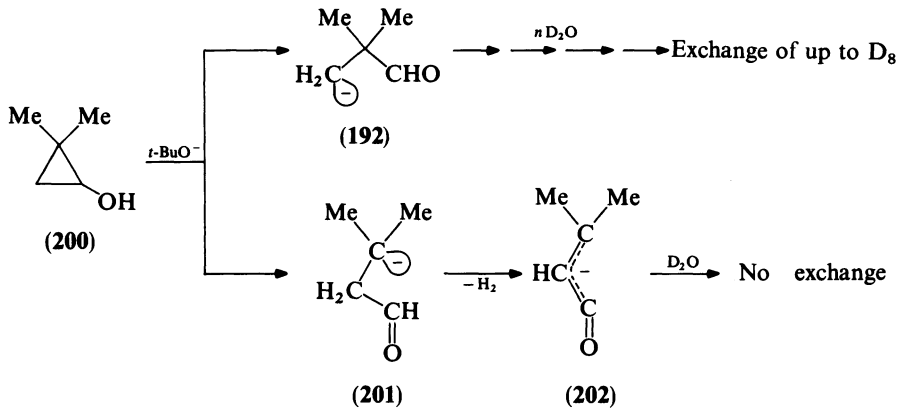
(193a)

In order to test such a suggestion various experiments were devised, and the central conclusion is that ring closure (or homoconjugation) *cannot* account for the remarkably low gas phase acidities of **191** and related compounds. The charge dipole interaction (**192**) seems to be of greater importance. It should also be mentioned that upon formation of the alkoxides of various substituted cyclopropanols there is a preference for *ring-opening*. For example, at most 20% of the anions generated from **194** remain ring-closed. The majority of ions undergo ring-opening and reprotonation, followed by deprotonation at a different site of the molecule to yield the most stable isomeric enol, as revealed from D-labelling studies (Scheme 29).



SCHEME 29

For 2,2-dimethylcyclopropanol (**200**) it was observed[112b] that deprotonation with *t*-BuO$^-$ yields a 3:2 mixture of two structures (**192**, **201**), which can be easily differentiated according to their distinctly different reactivity. The former undergoes with D_2O exchange of up to eight hydrogen atoms (as does **192** when generated from **191**), and the latter, after having lost H_2, yields an ion which does not exchange its hydrogen atoms (Scheme 30). Ring-opening was also demonstrated for the anion of *c*-$C_3H_5NH_2$[112b].



SCHEME 30

VII. IONIC PROCESSES OF CYCLOPROPENE DERIVATIVES

The gas phase chemistry of the cation radicals of C_3H_4 isomers, i.e. allene (**171**), propyne (**172**) and cyclopropene (**173**), has been studied intensively both theoretically and experimentally[114]. In a quite recent *ab initio* study[114], which was later confirmed experimentally[115]; it was predicted that ionized cyclopropene (**173**) will serve as the actual precursor for unimolecular H· loss from **171**–**173**, to generate the cyclopropenylium ion (**204**) irrespective of the constitution of the $C_3H_4^{+\cdot}$ precursor (Figure 6). Moreover, the calculations reveal that **171**, **172** and **173** are separated by high barriers which preclude easy isomerization. The minimal energy requirement path for the **171** ⇌ **172** isomerization proceeds via two successive 1,2-hydrogen migrations and involves the as yet

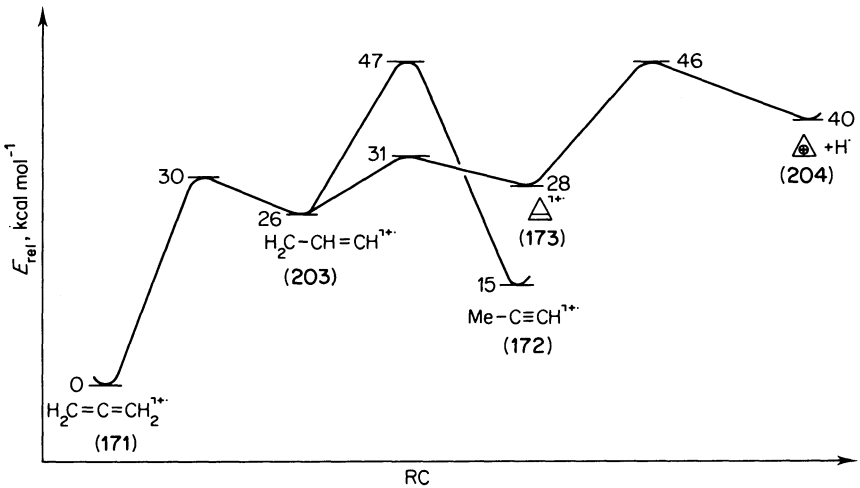
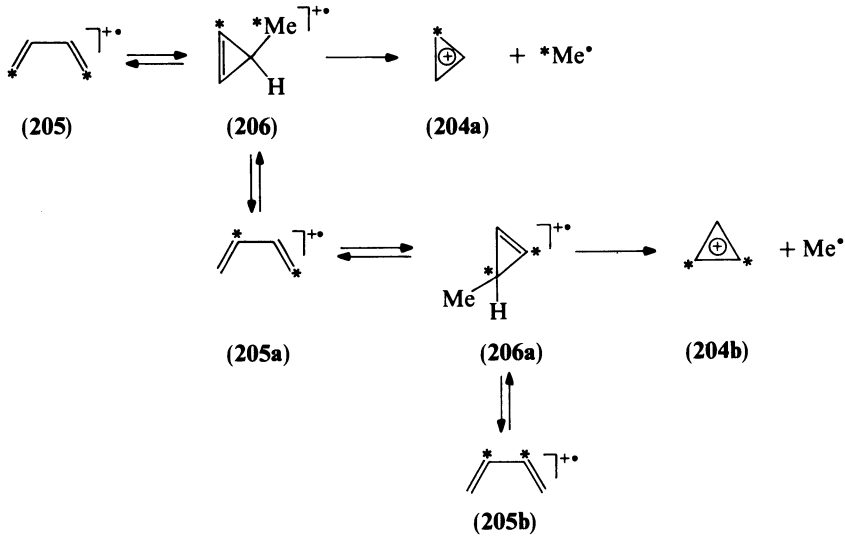


FIGURE 6. MERP, as obtained by 6-31G*//MNDO, for the isomerization of $C_3H_4^{+\cdot}$ and the dissociation to $C_3H_3^+ + H^\cdot$ (relative energies are given in kcal mol^{-1})

unknown stable species **203**, which serves also as the central intermediate for ring-closure to ionized **173**.

Three-membered ring formation precedes also $CH_3^{\bullet}$ loss from the molecular ion of butadiene (**205**)[116]. From specific D-labelling and using the field ionization kinetic technique the authors concluded that hydrogen atoms of **205** have been randomized completely at ion lifetimes as short as 10^{-11} s. The eliminated methyl radical then contains, however, more than 85% of the terminal carbon atoms as shown by ^{13}C-labelling. At longer lifetimes the internal carbon atoms also participate, but slowly, in methyl loss which becomes almost random to a large extent at 10^{-5} s. The following explanation (Scheme 31; an asterisk indicates a ^{13}C-labelled centre) has been offered[116]: in the time domain 10^{-11}–10^{-9} s the formation of 3-methylcyclopropene (**206**) is rate-determining, but at longer lifetimes successive ring-opening/ring-closure reactions become more competitive with direct methyl loss from ionized methylcyclopropene. For arguments that ionized cyclobutene cannot serve as a long-lived intermediate in the methyl elimination from **205**, the reader is referred to the original paper[116].



(205) (206) (204a)

(205a) (206a) (204b)

(205b)

SCHEME 31

For the $C_3H_3^+$ ions there is now ample theoretical[117] and experimental[118] evidence for the existence of four stable isomeric species, i.e. **204**, **207**–**209**. The aromatic cyclopropenylium ion **204**, known for quite a time, is the most stable form (ΔH_f^0 = 255 kcal mol^{-1}); the propargyl cation (**207**) has a heat of formation of ΔH_f^0= 281 kcal mol^{-1}, and these experimental values have adequately been reproduced by *ab initio* calculations[117a] where the difference in their ΔH_f^0 values was found to be 31 kcal mol^{-1}. Previous calculations[117b] indicated that two other structures were stable below the dissociation of lowest energy requirement to $C_3H^+ + H_2$ (ca. 378 kcal mol^{-1})[119], namely the prop-2-en-1-ylidene cation (**208**), having a predicted heat of formation of 325 kcal mol^{-1}, and the 1-propynyl cation (**209**) with a ΔH_f^0 value of ca. 368 kcal mol^{-1}. Recently, it was demonstrated experimentally[118c] that these four isomeric ions are indeed experimentally accessible and their characterization could be achieved by combining various techniques: Pure **204** was generated by only metastably fragmenting precursor ions of the composition C_4H_6,

C_3H_3Br and C_3H_3Cl. Pure propargyl cation (**207**) could be produced from the dissociative ionization of $HC{\equiv}CCH_2^{\bullet}$ in the ion source. The ions **208** and **209** were generated by collisionally induced charged inversion[120] of the corresponding anions. The latter were produced by dissociative electron capture and by gas phase reaction of OH^- with cyclopropene and $MeC{\equiv}CD$, respectively[109b, 121].

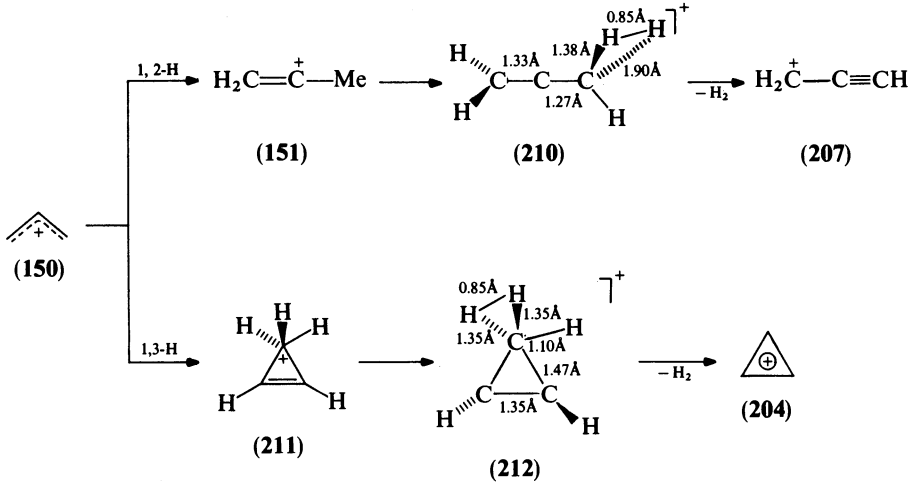
(**204**)

$HC{\equiv}C{-}\overset{+}{C}H_2$ (**207**)

$H_2C{=}CH{-}\overset{\bullet\bullet}{C}^+$ (**208**)

$Me{-}C{\equiv}C^+$ (**209**)

The generation of $C_3H_3^+$ ions by loss of H_2 from $C_3H_5^+$ has also been studied in great detail both experimentally[122] and computationally[123]. Using the MINDO/3 method Cooks *et al.*[123] studied the potential energy surface for loss of H_2 from the allyl cation (**150**). They found that the two lowest energy processes (Scheme 32) are of the 1,2- and 1,3-elimination type both of which commence by $2 \rightarrow 1$ and $3 \rightarrow 1$ hydrogen migrations, respectively. In the 1,2-elimination mode this involves isomerization of the allyl cation (**150**) to the 2-propenyl cation (**151**), while in the 1,3-elimination **150** first isomerizes to an intermediate, symmetrical corner-protonated cyclopropene (**211**). The reaction then proceeds by H_2-elimination from **151** via the carbonium ion transition state (**210**) to yield the propargyl cation (**207**) and from **211** via **212** to yield the cyclopropenylium ion (**204**), respectively. That loss of H_2 from $C_3H_5^+$ is a two-channel reaction is also indicated by the observation of a composite metastable peak[112, 118c].



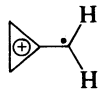
SCHEME 32

Derivatives of the cyclopropenylium ion have also been studied intensively. A few examples may serve as illustrations. For the open shell system $C_4H_4^{+\bullet}$, which is one of the major primary fragment ions produced in the unimolecular dissociation of many excited precursors, it is now well established[124] that there exist at least two stable species, the most stable one may have the methylenecyclopropene structure (**213**) and the less stable one may be an acyclic species, perhaps vinylacetylene (**214**).

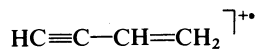
The methyl-substituted cyclopropenylium ion (**215**) was suggested to be generated from various $C_4H_8^{+\bullet}$ precursors, dissociating via consecutive losses of $H^{\bullet}$ and H_2[125].

Among the $C_3H_3O^+$ isomers studied[126] there was *no* evidence for the generation (or cogeneration) of the hydroxycyclopropenylium ion (**216**). Instead, three acyclic $C_3H_3O^+$ ions were generated and characterized, and these are the ions **217–219**, which have heats of formation of 179, 198 and 210 kcal mol^{-1}, respectively.

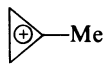
For the next higher homologue, $C_4H_5O^+$, in addition to the species **154–156** (Figure 4), three further stable structures (**220–222**) could be identified[127] by means of their characteristic unimolecular and collision-induced dissociations; quite surprising is the finding that the methoxy-substituted cyclopropenylium ion (**222**) is by 9 kcal mol^{-1} *less* stable than the methoxypropargyl cation (**220**), which is a reversal of stabilities observed for the $C_3H_3^+$ system (i.e. **204** and **207**).



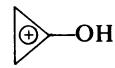
(**213**)



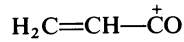
(**214**)



(**215**)

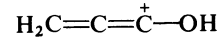


(**216**)

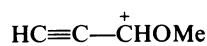


(**217**)

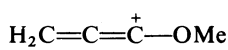
(**218**)



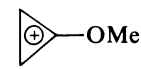
(**219**)



(**220**)



(**221**)

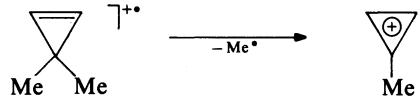


(**222**)

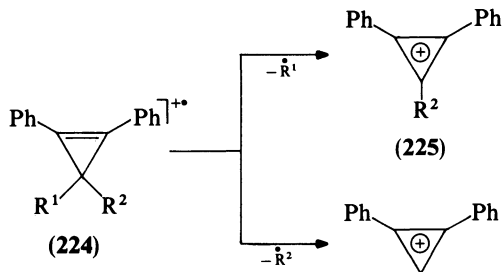
The base peaks in the 70 eV electron impact mass spectra of 3,3-dimethylcyclopropene (**223**)[128], 3-substituted 1,2-diphenylcyclopropenes (**224**)[129], 3-thiocyanato-1,2,3-triphenylcyclopropene (**227**)[130] and tri-*t*-butylcyclopropenyl azide (**229**)[131], just to mention a few examples, are often found to correspond to the loss of the (3)-substituent, thereby generating the substituted cyclopropenylium ions **215**, **225**, **226**, **228** and **230**, respectively (Scheme 33). It should be mentioned, however, that there exists at least one report[132] describing the complete absence of cyclopropenylium-type ions in 70 eV mass spectra of 1,2-dialkyl-substituted cyclopropenes. The reported spectra indicate that allylic cleavage seems to be operative, although no further experimental results are known which would lend support to such a suggestion.

Among the well-investigated family of $C_9H_7^+$ ions[133] it seems that the phenylcyclopropenylium ion plays a crucial role in both the formation of these ions from various C_9H_8 or $C_{10}H_{10}$ precursors as well as in the decomposition to $C_7H_5^+$ ions. However, like the subject of the $C_7H_7^+$ ions, the debate regarding the exact nature of the $C_9H_7^+$ ions seems to be unending. More definite conclusions must await further, more elaborate investigations.

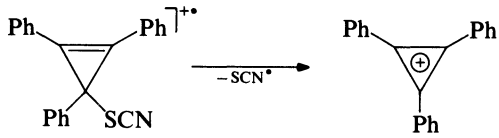
A similar situation prevails for the gas phase chemistry of $C_5H_7^+$ ions, for which quite a number of structurally different species are conceivable; among these are as the most fascinating ions **231–235** whose chemistry has been studied both experimentally[134,135] and computationally[135,148].



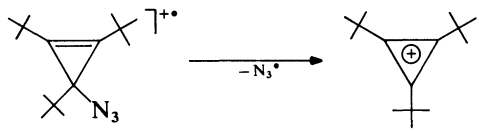
(223) (215)



(224) (225) (226)



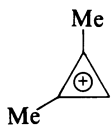
(227) (228)



(229) (230)

SCHEME 33

(231)



(232)

(233)

(234)

(235)

VIII. ACKNOWLEDGEMENT

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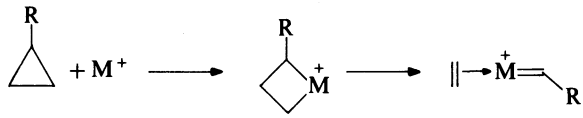
IX. ADDENDA

In a series of papers Gross *et al.*[136] provide experimental evidence that ionization of cyclopropane in the gas phase results in the formation of a trimethylene cation radical (**2**); isomerization of cold **2** to ionized propene (**3**) can be ruled out. The authors, moreover, stress that the structural changes of ionized cyclopropane in both the gas phase and in condensed phase[137] are entirely analogous.

The interactions of bare metal ions, M^+ (M^+ = Co, Fe) performed in an ion beam experiment, with cyclopropanes have also been studied in great detail. It has been demonstrated that reaction of Co^+ or Fe^+ with *c*-C_3H_6 or *c*-C_3H_5Me results initially in the formation of metallacyclobutanes (**236**). The latter rearrange to olefin/carbene complexes (**237**)[138] (Scheme 34).

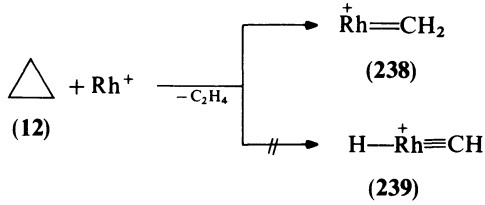


(**12**) (**236**) (**237**)

R = H, Me

SCHEME 34

In the gas phase reaction of Rh^+ with *c*-C_3H_6, among other processes, elimination of C_2H_4 has been observed and the resulting metal ion was shown to have the structure of a methylidene–rhodium complex (**238**) instead of a hydrido-methylidene species (**239**)[139]. $RhCH_2^+$ (**238**) reacts readily with H_2 and CH_4 and represents the first example of methane activation by a cationic mononuclear transition-metal complex in the gas phase. Reactions of both $Rh{=}CH_2^+$ and its analogues $Fe\text{-}CH_2^+$ and $Co\text{-}CH_2^+$ with cyclic hydrocarbons were studied, and it is assumed that in the initial step metallacycloalkanes are generated[140] (Scheme 35).



(**12**) (**238**) (**239**)

SCHEME 35

With regard to the formation of ionized cycloalkanes as intermediates in gas phase processes (Section IV), Holmes *et al.*[141] conclude from using labelled precursors and performing energetic measurements as well as charge stripping reactions that H_2O loss from ionized 1-propanol yields in a highly specific 1,3-elimination nearly exclusively *c*-$C_3H_6^{+\cdot}$. Cyclopropane-like intermediates, in particular ring-opened species of trimethylcyclopropane molecular ions, are believed to play a role in the methyl loss from ionized 4-methyl-2-pentene and 2-methyl-2-pentene[142]. The conclusion is mainly based on the study of D-labelled precursors and it remains to be established by using ^{13}C-labelled precursors to unravel the details of the skeletal isomerization.

The repeatedly noted ring-opening of ionized cyclopropane derivatives (Section III.A) seems also to account for the randomization of methoxy groups in ionized dimethyl 2-methoxy-3,3-dimethylcyclopropane-1,1-dicarboxylate[143]. Similarly, the electron impact and chemical ionization mass spectra of benzoylcyclopropanes can be interpreted by ring-opening followed by facile 1,2-hydrogen migration, which precede the main dissociations[144].

Smith *et al.* have recently shown[145] that the gas phase reaction of hydrogen with $C_3H_2^{+\cdot}$, to give $C_3H_3^+ + H^\cdot$, generates exclusively the propargyl ion $HC{\equiv}CCH_2^+$ (**207**) and *not* the thermochemically more stable cyclopropenylium ion (**204**), although the latter process would be more exothermic. This surprising result has been interpreted as evidence for a linear structure of the $C_3H_2^{+\cdot}$ precursor which upon formation of an $C_3H_2^{+\cdot}/H_2$ encounter complex does not have the internal energy to undergo skeletal reorganization.

A further study aimed to distinguish isomeric $C_3H_3^+$ ions was reported by Köppel and McLafferty[146]. Using appropriately labelled precursors and analysing the collision induced dissociation pattern the authors present evidence for the existence of several non-interconverting $C_3H_3^+$ species, including **204** and **207**.

In a very detailed study, using a combined theoretical/experimental approach, Squires *et al.*[147] examined the gas phase properties of isomeric $C_3H_5^-$ anions. They were able to generate stable alkyl, 2-propenyl, 1-propenyl and cyclopropyl anions, as well as parent vinyl anions, in the gas phase by collision induced dissociation of the corresponding carboxylate anions, using the reaction sequence in Scheme 36 which was monitored by Fourier transform mass spectrometry.

$$R{-}CO_2SiMe_3 \xrightarrow[-SiMe_2NH_2]{NH_2^-} RCO_2^- \xrightarrow[-CO_2]{CID} R^-$$

SCHEME 36

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CHAPTER 5

Photoelectron spectroscopy

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I. PHOTOELECTRON SPECTROSCOPY

In its simplest form, photoelectron spectroscopy consists in irradiating the specimen with monochromatic light or X-radiation of sufficient energy to eject electrons from the electronic orbitals of interest, passing the resultant photoelectrons through an electron energy filter and plotting the photocurrent so obtained as a function of the pass energy of the filter. The ionization energy of the specimen is obtained from Einstein's equation:

$$h\nu = I + \varepsilon \tag{1}$$

The primary process involved is no more than the ordinary photoelectric effect:

$$M + h\nu = M^+ + e^- \tag{2}$$

M in equation 2 can be either solid, liquid or gaseous in form and might be an atom, ion or molecule. In this review only gases are considered. Energies will be given in eV,

e.g. ionization energies I, electron kinetic energies ε and photon energies $h\nu$. In the ultraviolet branch of the subject the most common source of ionizing radiation is the helium discharge lamp which produces copious amounts of He(I) radiation of energy 21.22 eV and small but still useful amounts of He(II) radiation of energy 40.81 eV; such lamps consist of a volume of the gas at low pressure through which an electrical discharge is struck and maintained at a few milliamps and several hundred volts (larger voltages usually being required at the start). Since few materials transparent to radiation of such an energy exist (very thin aluminium foil can be used[1]) it is customary to use windowless lamps, with the result that some helium escapes from the lamp into the sample compartment but this is rarely an inconvenience since the necessity of evacuating the sample compartment for another reason implies that the amount of helium present is usually insignificant. On the other hand, some contamination of the lamp by the sample gases can occur and frequently shortens the period during which the lamp can be run between replacement of the anode parts. Apart from helium, the other noble gases can also be employed but the energy of the radiation diminishes with increasing atomic number and, below about 20 eV, the photoelectric effect begins to relinquish first place in importance to autoionization:

$$M + h\nu \rightarrow M(\text{excited}) \rightarrow M^+ + e^- \qquad (3)$$

The heavier noble gases also give rise to problems of internal corrosion caused by their sputtering action on the lamp anode. The ideal radiation source is the synchrotron, having the advantage of an unrestricted range of energy. Unfortunately, being large and costly installations, synchrotrons are available to few laboratories.

The two-step process of equation 3 (alternatively called either autoionization or preionization) is dominant over the photoelectric effect below values of $h\nu$ of about 10 eV on account of the high probability of the first step, giving an electronically excited state which subsequently relaxes either by ionization, as illustrated above, or by fluorescence, dissociation, transfer of energy to some acceptor, etc.

Since electrons cannot pass without energy losses due to collisions through a few cm of gas at atmospheric pressure it is necessary to evacuate the electron path from the sample to the detector; a rule of thumb says that the product of pressure times path length should not exceed 1 cm torr. Multiplicative electron detectors like channeltrons require vacua of 10^{-4} to 10^{-6} torr or better, dependent on the type, but the study of solid surfaces requires much lower pressures, say 10^{-10} torr, in order to give the experimenter sufficient time to obtain spectra of the pure surface before it becomes contaminated by the gases in the sample compartment.

Ionization processes of different energy can be observed in the plot of photocurrent against electron kinetic energy which constitutes a photoelectron spectrum but since the technique does not provide an absolute measurement of ionization energy it is often necessary to calibrate the spectrum. The usual method of calibration of a gas is to add to the sample some calibrant gas whose ionization energies are known, from Rydberg spectroscopy for example, and it is important that this should be done with a mixture of calibrant and sample gases so that a superimposition of calibrant spectrum on sample spectrum is obtained; otherwise, since photoelectron spectrometers are found to be sensitive both to pressure changes and to change of sample gas, the energy scale will not be fixed.

Many types of electron energy filter or analyser exist. Perhaps the commonest is the hemispherical condenser although a commonly used commercial instrument is based upon the 127° cylindrical condenser[2].

The structure to be found in photoelectron spectra consists of bands or lines corresponding with the ejection of electrons from different molecular orbitals whose

energies, E, are related to the ionization energies by Koopmans' approximation:

$$I = -E$$

Molecular vibrations and, very rarely, rotations cause the appearance of fine structure upon the molecular bands.

A major complication occurs when more than one electron is promoted during the photoelectron process, rather as if the two stages of equation 3 above take place simultaneously so that one electron occupies a formerly unoccupied or partially occupied orbital whilst the other breaks free from the molecule altogether. This situation is encountered for example in the He(I) photoelectron spectrum of cyclopropene where the intensity of the bands from the fifth onwards is reduced by admixture with two-electron processes. Thus the peak in the He(I) photoelectron spectrum at 16.68 eV ($5a_1$, Section III) has been assigned to the ionization of an orbital of $5a_1$ type in a process mixed with simultaneous ionization and promotion to the π^* level of electrons from the uppermost pair of occupied orbitals[3]; at higher ionization energies the intensities of the bands become scattered over numerous processes and the bands become barely detectable. The 16.68 eV peak is due partly to

$$\ldots (5a_1)^2 \ldots (3b_2)^2\ (2b_1)^2 \rightarrow \ldots (5a_1)^1 \ldots (3b_2)^2\ (2b_1)^2 + e^- \qquad (4)$$

and partly to

$$\ldots (5a_1)^2 \ldots (3b_2)^2\ (2b_1)^2 \rightarrow \ldots (5a_1)^2 \ldots (3b_2)^1\ (2b_1)^1\ (\pi^*)^1 + e^- \qquad (5)$$

Although two-electron processes have a lower probability of occurring than one-electron processes they are nevertheless commonly found at ionization energies of 10 eV or so above threshold. As a consequence the rule that one orbital produces one band in the spectrum (possibly with fine structure) breaks down and the expected peak is either accompanied by a number of subsidiary peaks, all robbing it of intensity, or if there happens to be a sufficiently great number of configurations close in energy the primary peak cannot be found at all, its intensity spread over a wide range. Fortunately configuration interaction is usually absent near threshold, the region of greatest interest to the organic chemist and in truth the bands following after the first few are generally so vitiated by overcrowding and superposition that they are of no benefit in any case. With few exceptions therefore this review will concern itself only with the threshold region.

Simple photoelectron spectroscopy of the type described above gives information about the nature of the electronic states, the ionization energies of the subject and the relative cross-sections of ionization. Combined with other techniques in coincidence, photoelectron spectroscopy also gives spectroscopic information about ions in specific energy states; when combined with mass spectroscopy for example, information is derivable about the manner of fragmentation of the ions generated by the photoelectric effect. The apparatus required for photoelectron/photoion coincidence is a photoelectron spectrometer coupled with a mass spectrometer and coincidence electronics capable of measuring the time lapse between the recording of the photoelectron and the arrival of the ion at the detector after its passage through the mass spectrometer[4] (Section IV).

Little work has been done on the X-ray photoelectron spectroscopy of the cyclopropyl group but it has been applied to cyclopropane itself as a reference compound of zero ionicity in a study of the percentage ionicities of methyl lithium CH_3Li and dilithiomethane CH_2Li_2[5].

The Auger spectra of cyclopropane and related molecules are given in Figure 1. These spectra give the energies of electrons arising from the relaxation of the carbon atoms with a

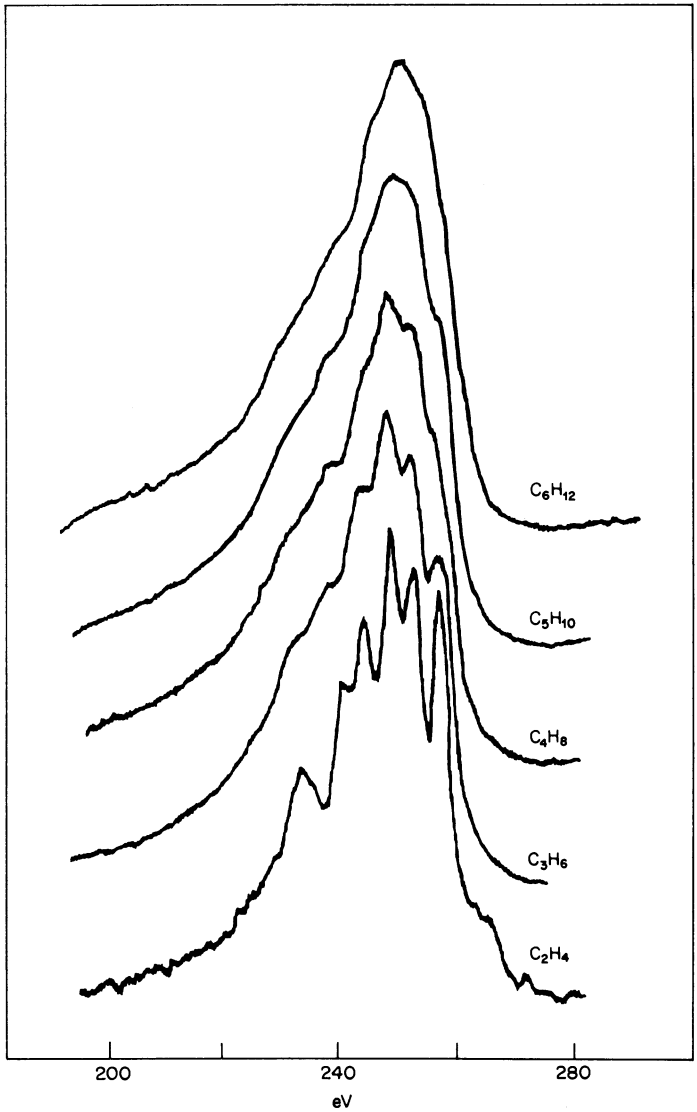


FIGURE 1. The Auger spectra of ethylene, cyclopropane, cyclobutane, cyclopentane and cyclohexane[6] in the gas phase showing the carbon (K, valence, valence) region excited by electron bombardment

hole in the K shell caused by electron bombardment:

$$C(ls^2 2s^2 2p^2) + e^- = C^+(1s^1 2s^2 2p^2) + 2e^-$$

$$C^+(1s^1 2s^2 2p^2) = C^{2+}(1s^2 2s^1 2p^1) + e^-(\text{Auger})$$

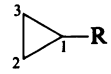
The Auger electron in the above process results as a valence electron drops down into the

K shell. Because the energies of the valence electrons vary with the chemical bonding of the carbon atom it is found that Auger spectra also depend upon the chemical state of the atom. From the figure it is clear that the structure in the Auger spectrum of cyclopropane is intermediate between that of ethylene and the higher saturated paraffin ring compounds but it is impossible to say much more than this at present since the multi-electron nature of the Auger process is too complex. Although Auger spectra make a good analytical tool, especially for the study of the solid surface, they are not readily interpretable[6].

II. CYCLOPROPANE

Like UV absorption spectroscopy[7], UV photoelectron spectroscopy readily gives information about the degree of conjugation and it happens that in this respect cyclopropane is atypical of the homologous series of which it is the smallest member[8-10]; thus the cyclopropyl group has an unusual propensity to conjugate with centres of unsaturation and other types of electron acceptor. Some non-spectroscopic evidence claimed for the enhanced hyperconjugative powers of the cyclopropyl group is given below.

1. Cyclopropyl chloride has a dipole moment of 1.76 D compared with 2.04 D in cyclopentyl chloride[11].
2. If R is a π acceptor in **1**, e.g. C=O, C=C, Ph, N=C or N=N, then the 2–3 bond is increased in length (say by a distance *D*) whilst the other bonds (1–2 and 1–3) are reduced in length by about half as much (i.e. by *D*/2)[12].



(1)

3. The cyclopropyl group is often equivalent to the vinyl group (–CH=CH_2); thus the exocyclic bond length in **1** is abnormally short and not far from the C–R bond length found in CH_2=CH–R[12] (R = vinyl, carbonyl, acid and ester groups).

The valence molecular orbitals of cyclopropane accessible to the helium lamp are 18 in number; derived from H(1s) (13.6 eV), C(2s) (19.5 eV) and C(2p) (10.7 eV), they span the following irreducible representations of the D_{3h} point group.

1. $a_1' + e'$ from C(2s).
2. $2e' + a_1' + a_2'$ from C($2p_x$) and C($2p_y$).
3. $e'' + a_2''$ from C($2p_z$).
4. $a_1'' + a_2'' + e'' + e'$ from H(1s).

A number of SCF molecular orbital calculations for cyclopropane have been reported, among them those of Skancke[13], Kochanski and Lehn[14], Kao and Radom[15], Hase and colleagues[16], Basch and colleagues[17], Collins and Gallup[18] and von Niessen and colleagues[19]; the most accurate appear to be those of Skancke (Table 1).

Electron density contour diagrams have been derived[14,21] (Figure 2) and potential energy curves and surfaces calculated[18,22]. In addition to this impressive quantity of accurate work on the parent compound a number of simplified schemes were proposed by Forster[23], Coulson and Moffit[11,24] and by Walsh[25,26]; these schemes have been widely employed for the interpretation of the photoelectron spectra and other properties of the derivatives of cyclopropane.

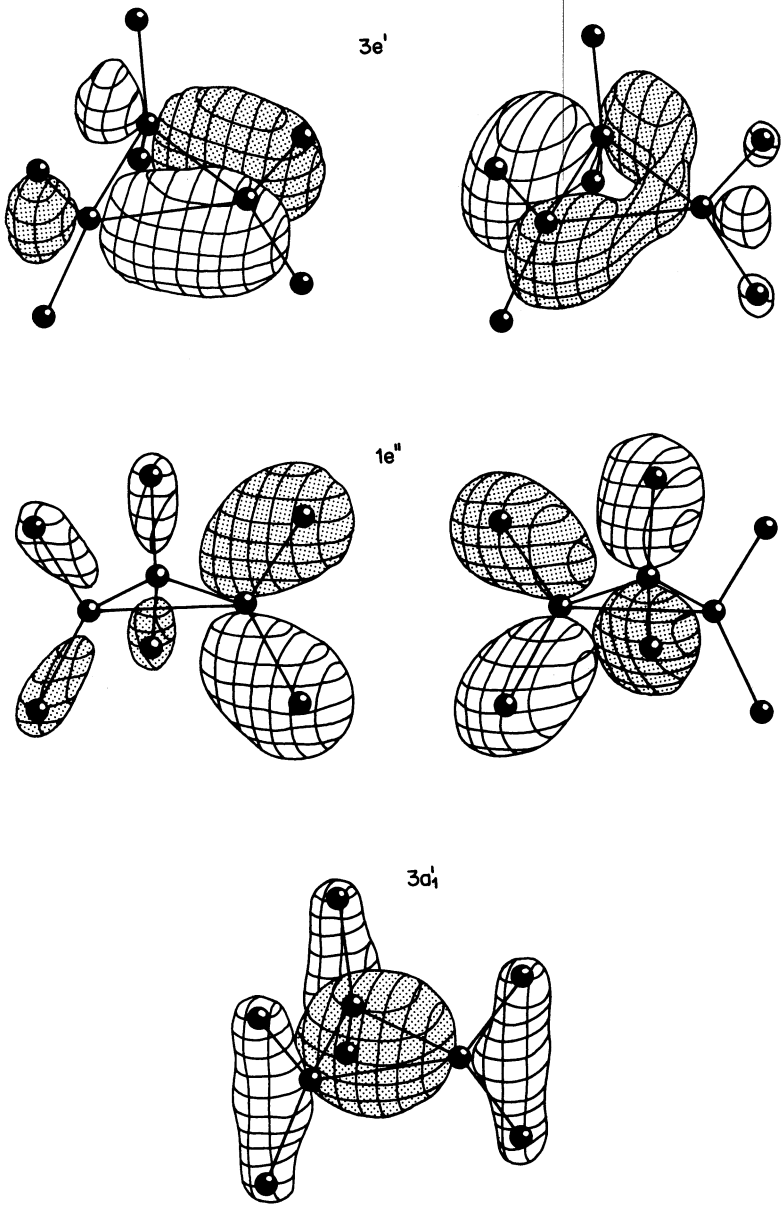


FIGURE 2.

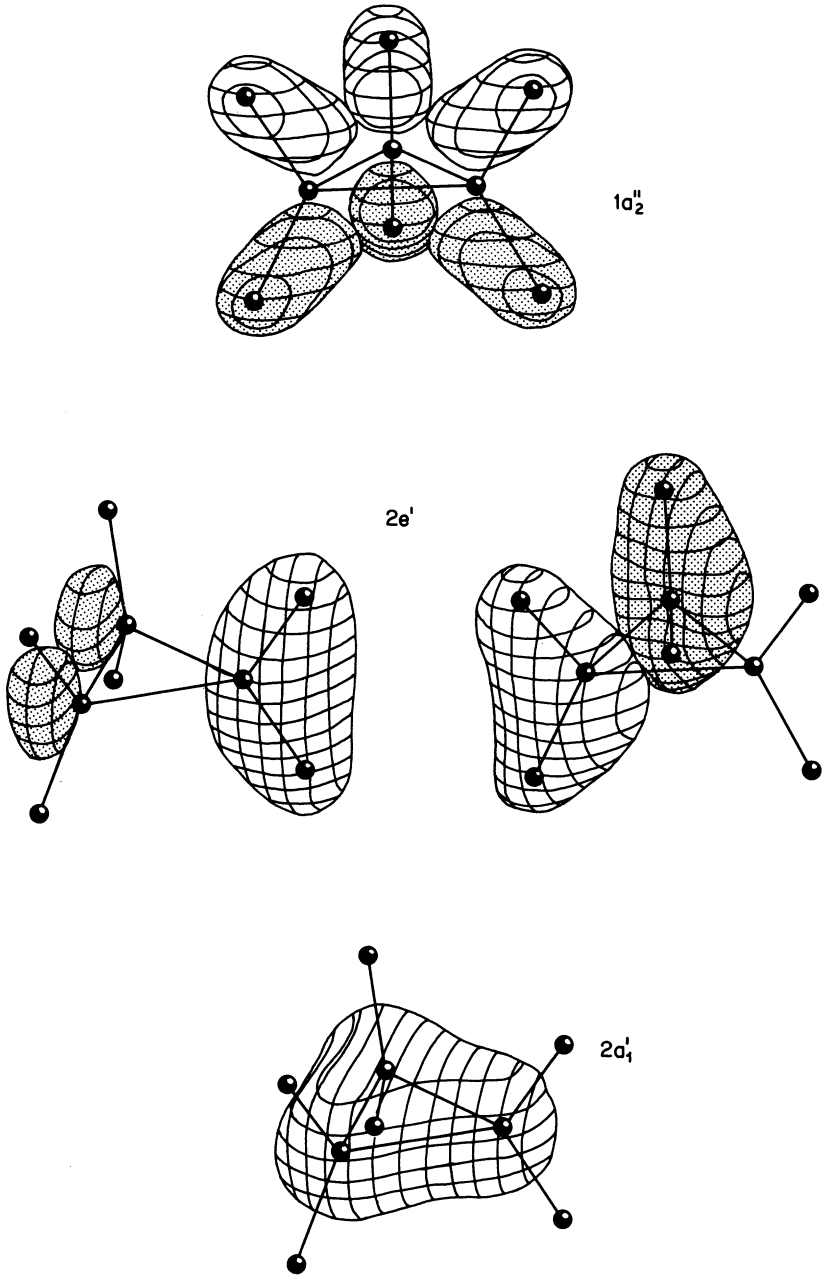


FIGURE 2. Electron density surface contours for the occupied orbitals of cyclopropane derived from an SCF calculation[21]. The individual figures are in order of energy, the highest at the top of the facing page

TABLE 1. Energies of the molecular orbitals of cyclopropane E (in eV) calculated by the SCF method, together with their irreducible representations in the D_{3h} point group and the vertical ionization energies I (in eV) derived from the He(I) photoelectron spectra of the vapour

	E[14]	E[13]	E[17]	I[20]
$1a_1'$	−306.17	−305.79	−305.56	
$1e'$	−306.13	−305.76	−305.53	
$2a_1'$	−31.05	−31.02	−31.03	
$2e'$	−22.40	−22.35	−22.19	
$1a_2''$	−18.61	−18.35	−18.29	16.75
$3a_1'$	−16.70	−17.07	−16.95	15.71
$1e''$	−14.35	−14.11	−13.89	13.0
$3e'$	−11.51	−11.59	11.40	10.6 and 11.3
$4e'$	—	6.98	6.55	
$4a_1'$	—	7.65	7.26	
$1a_2'$	—	8.18	7.69	

A. The Coulson–Moffit and Walsh Models of the Molecular Orbitals of Cyclopropane

The Coulson–Moffit and Walsh models of the cyclopropane orbitals have been used since the 1940s but there has been some argument about which, if either, provides an adequate description of the facts. Walsh's model has been the more popular because it is perhaps easier in concept and also because it was believed that the models are equivalent[27], although it was pointed out that they were not at the very outset[11]; more recent studies have particularized the differences[28,29].

Both models start with C(2s) and C(2p) orbitals which are first hybridized[30,31] and then combined to form molecular orbitals:

$$\psi \text{ (molecular)} = \sum_i C_i \psi_i \text{ (hybrid)} \tag{6}$$

Equation 6 is merely a statement of the linear combination of atomic orbitals (LCAO) approximation.

In the Walsh treatment sp^2 hybrids are formed, three per carbon atom, of which two are directed out of plane to form C–H bonds and one is left in the plane of the ring and directed towards the centre so as to bisect the C–C–C angle (Figure 3). This treatment leaves one C(2p) orbital lying in the plane of the ring, unhybridized and perpendicular to the sp^2 hybrid directed at the ring centre.

In the Coulson–Moffit treatment[11,24] all four atomic orbitals of carbon are hybridized and the resulting orbitals, something between sp^3 and sp^2 in character, are divided into pairs, one in the plane of the ring and the other pointing out of plane so as to engage the H(1s) orbitals and form C–H bonds. The strain in the ring is taken into account by optimising the degree of hybridization (using the variation theorem) so as to give the in-plane orbitals the largest possible amplitude in the directions of the C–C bonds hence obtaining the strongest linkage possible. This method of optimization does not generally result in the maximum density pointing in the direction of the C–C bond and in cyclopropane the in-plane orbitals are directed at 22° to the C–C bond (Figure 3) according to Coulson and Moffit.

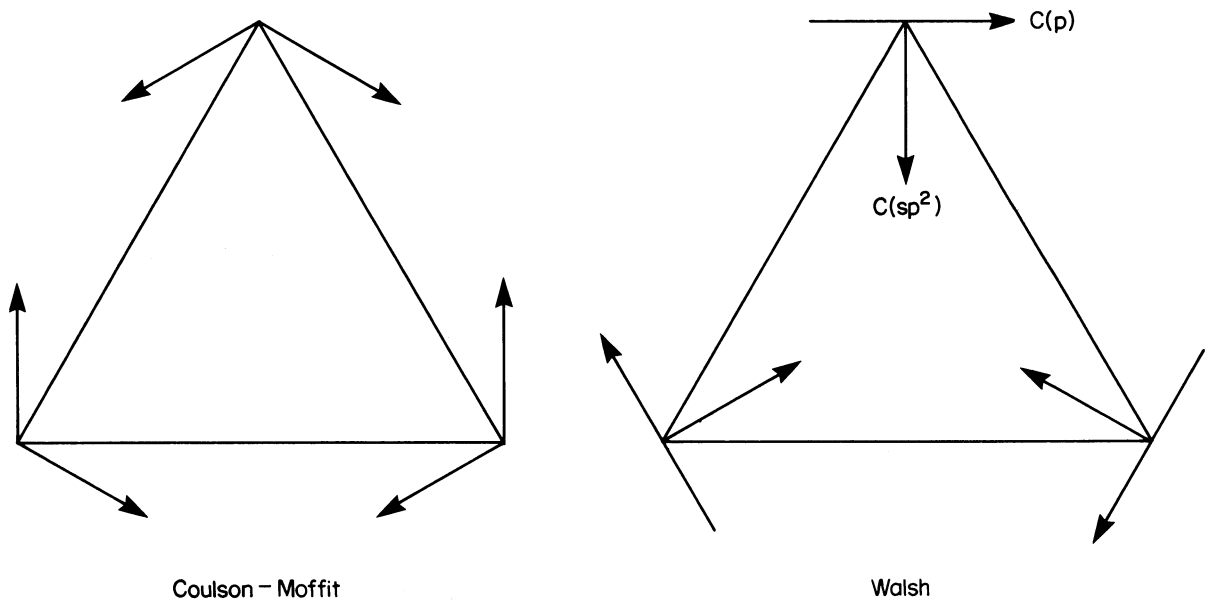


FIGURE 3. Alternative hybridization schemes: in the Coulson–Moffit model the hybridization state is between sp^2 and sp^3 and the maxima of the orbitals in the plane of the ring are directed at 22° to the C–C bonds. In the Walsh model there are sp^2 hybrid bisecting the C–C–C angles and, perpendicular to these, unhybridized C(2p) orbitals; all these orbitals being in-plane

In both models the molecular orbitals deriving from carbon and lying in the plane of the ring form a set consisting of three bonding and three antibonding orbitals depicted in Figure 4. Note that in the Walsh model the bonding orbitals of e′ symmetry contain no content of hybridized orbitals. Since both models employ the same basis of atomic orbitals

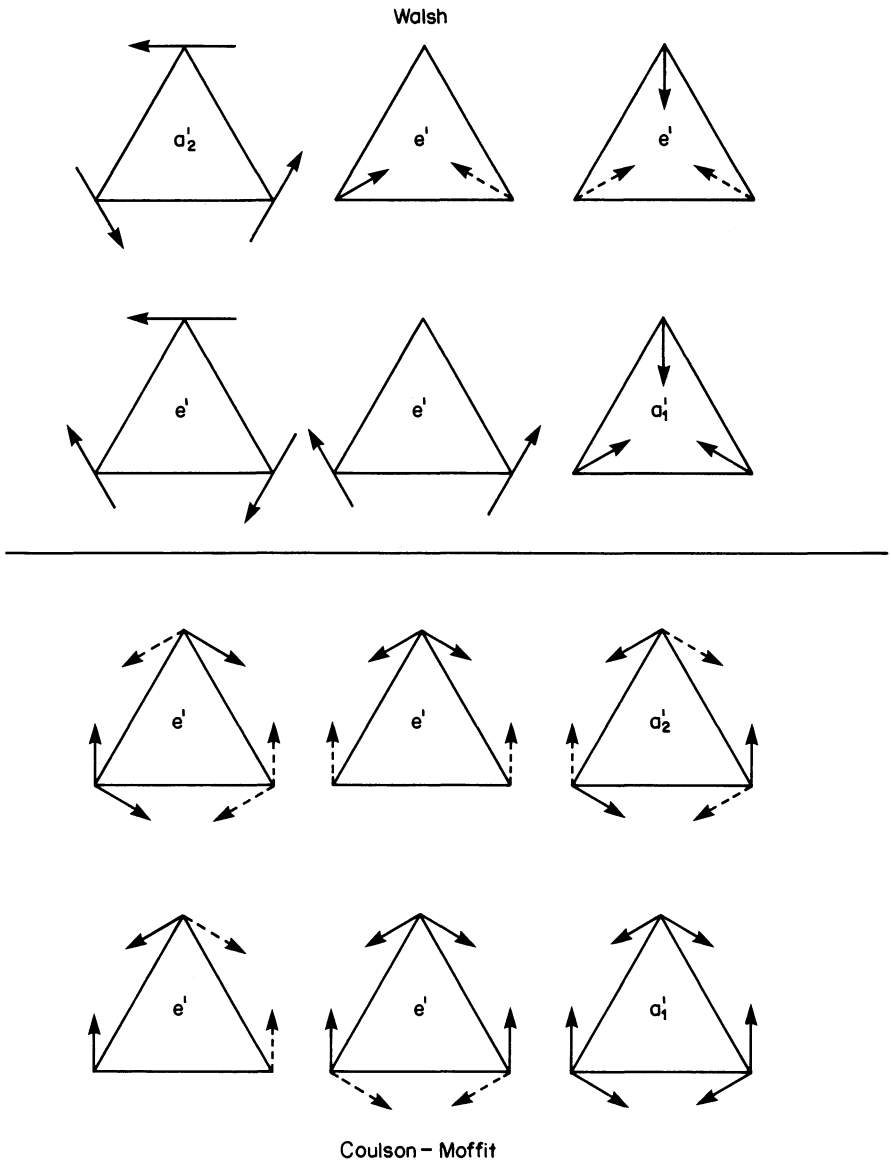


FIGURE 4. Showing how molecular orbitals of the Coulson–Moffit and the Walsh models are made up by the linear combination of atomic orbitals of Figure 3. For each model the upper trio of symmetry e′ and a_1' is antibonding and the lower is bonding

they must be equivalent at this level[28, 29] but the molecular orbitals of Figure 4 are not equivalent. The electronic density contours of the sum of the SCF orbitals corresponding to the bonding set $e' + a_1'$ (here labelled 3e′ and $2a_1'$) bear a marked resemblance to Coulson and Moffit's result (Figure 5) whose model[11] is therefore supported, if not conclusively. Noting that the maximum density of electrons in their model was not positioned exactly between the nuclei of the C–C bond (i.e. the bond was 'bent') Coulson and Moffit reported that the bending angle was 22°, the recent SCF result is only 5° [14]. Another feature common to the Coulson–Moffit and the SCF results is the presence of a shallow central depression in the electronic density distribution[10].

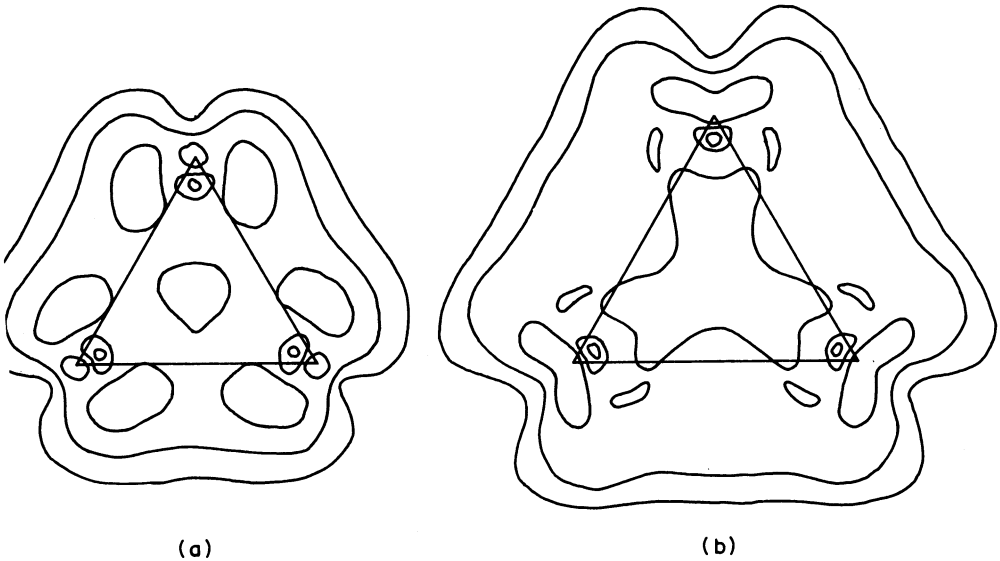
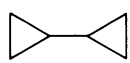


FIGURE 5. Electronic density contours in the plane of the ring of cyclopropane. A, an accurate, SCF result[14] showing the sum of the electronic densities of orbitals $2a_1'$ and 3e′. B, Coulson and Moffit's result[24] showing the sum of the densities of the bonding orbitals given by their model (Figure 4). In both instances the electronic density maxima lie outside the ring (the bond therefore being 'bent') and there is a central minimum.

Heilbronner and his colleagues have shown[28, 29] that the energies of the Walsh orbitals of e′ symmetry are not equal to those of the Coulson–Moffit scheme, further that the energy difference between the bonding and the antibonding Walsh orbitals of e′ symmetry is too low so that minimization of the energy (by the variation theorem) leads to final molecular orbitals containing a large proportion of the original antibonding Walsh orbitals. Gleiter[9], for example, found it necessary to incorporate in the bonding orbitals some 20% of the antibonding Walsh orbitals of e′ symmetry in order to reproduce by the Walsh method SCF calculation of the dependence on dihedral angle of the energies of bicyclopropyl and tricyclopropyl derivatives (**2** and **3**). The superiority of the Coulson–Moffit model therefore seems to be established.



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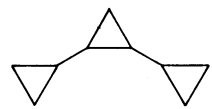

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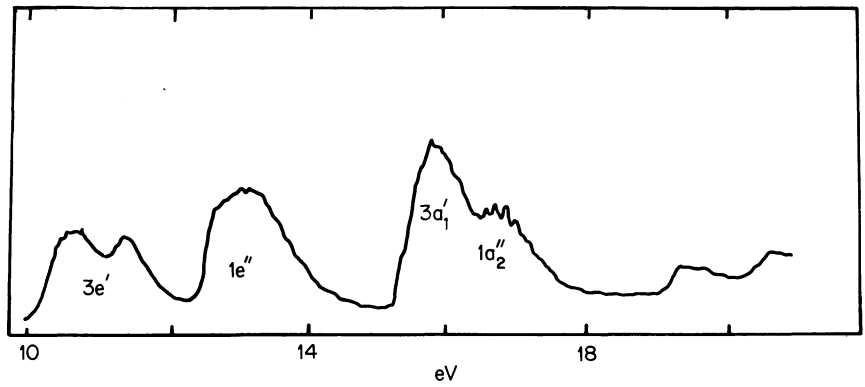


FIGURE 6. The He(I) photoelectron spectrum of cyclopropane[20]. A large Jahn–Teller splitting is evident in the pair of bands labelled 3e′ and a smaller one is suggested by the shape of the 1e″ band. Koopmans' theorem is assumed to give the correct sequence of ionization energies

The He(I) photoelectron spectrum of cyclopropane is given in Figure 6 (see also Table 1).

Koopman's approximation[32], as was mentioned in Section I, equates the ionization energy of an orbital with the negative value of the orbital energy given by the Hartree–Fock equations[33, 34] but in fact this would be true only if all the orbitals of the ionised system (M^+ in equation 2) were the same as those in the original system (M), a condition which is not obeyed even within the very short time scale of the photoelectric effect since, as the photoelectron leaves, the remaining electrons experience the loss of the electron–electron repulsions and screening of the nuclear charge accountable to the departing particle. Ionization energies can be accurately calculated by means of equation 7:

$$I = -(\text{total energy of M}) + (\text{total energy of } M^+) \tag{7}$$

but this necessitates a complete molecular calculation for every ionization energy.

In systems where the molecular orbitals have a similar atomic basis, as in the molecules discussed in this review, it is usually found that the *sequence* of ionization energies and orbital energies is the same although the absolute values do not agree, as for example in Table 1. Should there be a discrepancy in sequence there is said to be a 'failure of Koopmans' theorem', examples of which are common especially for molecules where the atomic bases differ as, for instance, in organometallic compounds like ferrocene and bis-(π-allyl)nickel[35–37]. Further examples can be found in Refs 38–44.

Although in D_{3h} symmetry the 3e′ orbital of cyclopropane is degenerate a doublet is found in the spectrum (Figure 6); that this might be due to the operation of the dynamic Jahn–Teller effect was first suggested in 1969[14, 15] and in fact the triangular molecule had attracted theoreticians for some time as a model for their calculations on the dynamic Jahn–Teller effect[45, 46]. In general the dynamic Jahn–Teller effect is caused by the coupling of vibrational and electronic motions of molecules, leading to the breakdown of the Born–Oppenheimer principle with the result that degeneracies based upon symmetry are raised by certain vibrational motions which lower the symmetry. Thus if Q is the vibration responsible and G is the original point group, lowered to S by the vibration

$$G \xrightarrow{Q} S$$

then the lower group S is such that the vibration is totally symmetric in S or, if Q has

more than a single dimension, then at least one dimension of Q is symmetric in the point group [47-49].

In cyclopropane $G = D_{3h}$ and the active vibrations Q belong to the irreducible representation e′ so that

$$D_{3h} \xrightarrow{e'} C_{2v} \xrightarrow{b_2} C_s$$

The above descent in symmetry is caused by the e′ vibrations which become $a_1 + b_2$ in C_{2v} and 2a′ in C_s.

The point group C_{2v} is an *epikernel* of e′ in D_{3h} and C_s is the *kernel* of e′ in D_{3h}, an epikernel being a group in which one or more components of the vibration remains active. The e′ vibrations of cyclopropane can alternatively be expressed as $(x, y, x \pm iy)$ or $R\exp(\pm i\phi)$ where x and y are vectors in the plane of the ring, $i = \sqrt{-1}$, R is a numerical constant and ϕ is the angle of rotation about the axis of symmetry; they give the molecule the quality of a rotatory oscillator in which a distortion of the C–C–C bond angle circulates around the carbon plane (Figure 7). The distortion of the bond angle lowers the symmetry from D_{3h} to C_{2v} with effects on the orbital energies which can be seen in the Walsh diagram (Figure 8): both 3e′ and 1e″ being split although only the first of these

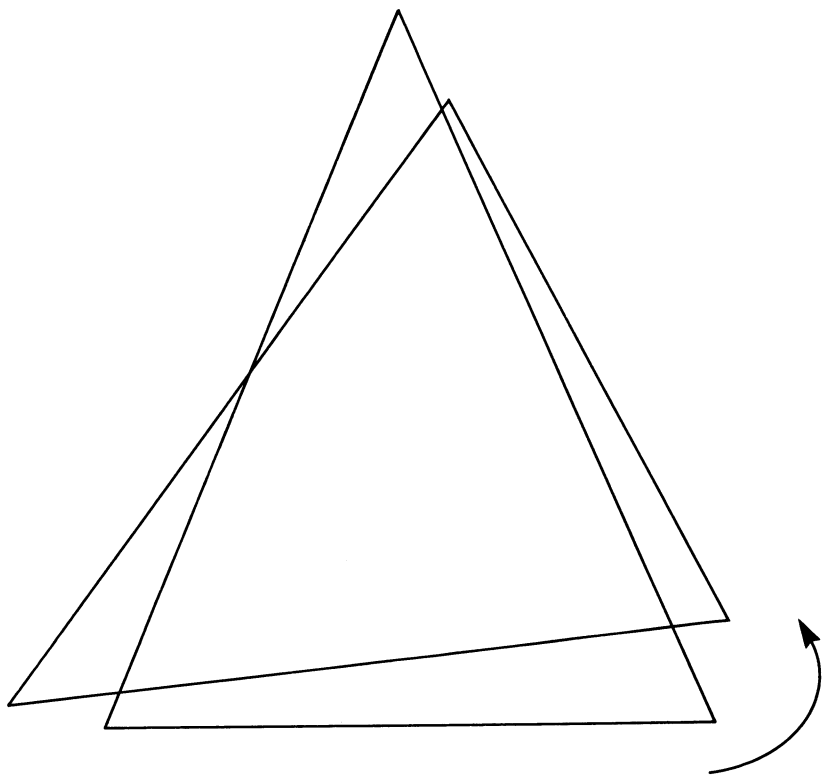


FIGURE 7. The effect of e′ vibrations on the cyclopropane molecule is to make it a rotatory oscillator in which a bond angle distortion moves successively from atom to atom round the ring.

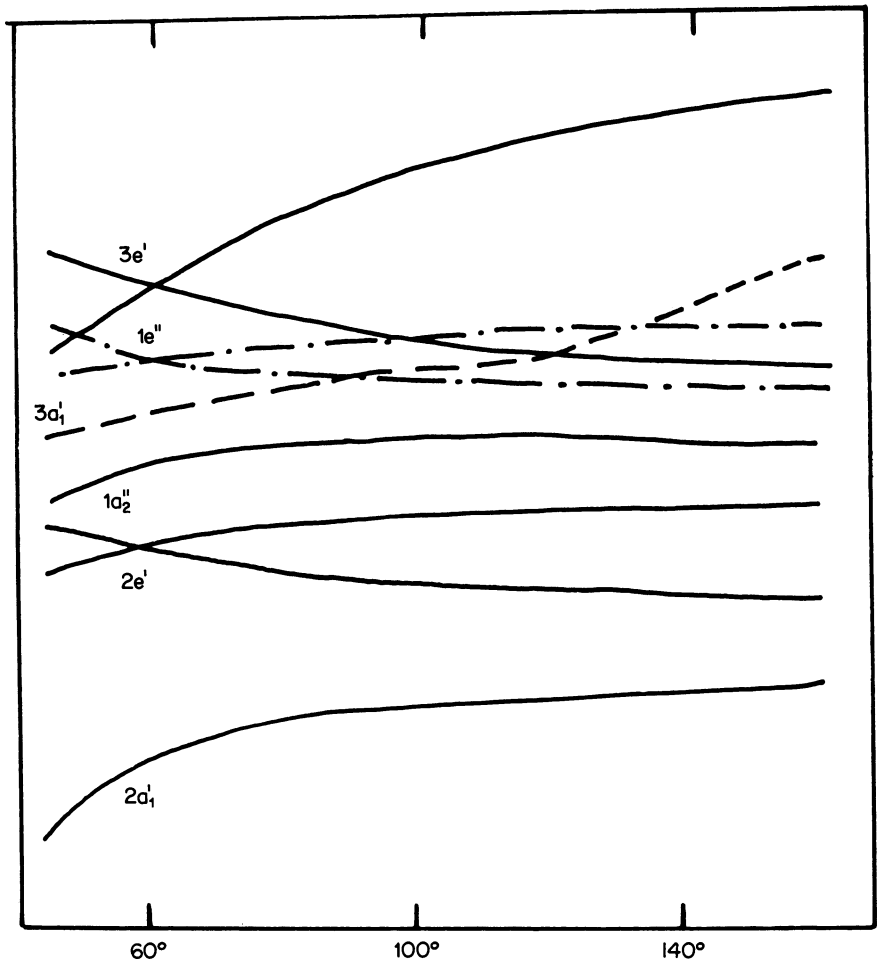


FIGURE 8. Walsh diagram for cyclopropane[22] showing how the energies of the occupied electronic orbitals respond to a distortion of the C–C–C bond angle, lowering the symmetry from D_{3h} to C_{2v}. Some lines are broken for the sake of clarity

appears in the spectrum as a resolved doublet (e′ becoming $a_1 + b_2$ and e″ becoming $a_2 + b_1$). A number of calculations have been reported on the energy separation of the orbitals as a consequence of the Jahn–Teller effect[18,49–51], Longuet-Higgins[46] gives the electronic potentials of the two branches of the e orbitals by equation 8:

$$U, U' = \tfrac{1}{2}\lambda r^2 \pm kr \tag{8}$$

where λ is the Hook's law coefficient for the Jahn–Teller active vibration and k is a coefficient for the corresponding change in orbital energy when the distortion has magnitude r. At the bottom of the troughs (Figure 9) the potential energy is $-\frac{1}{2}k^2/\lambda$ relative to the energy at the origin. The zero point energy of the vibration is $\hbar\sqrt{\lambda/M}$ where

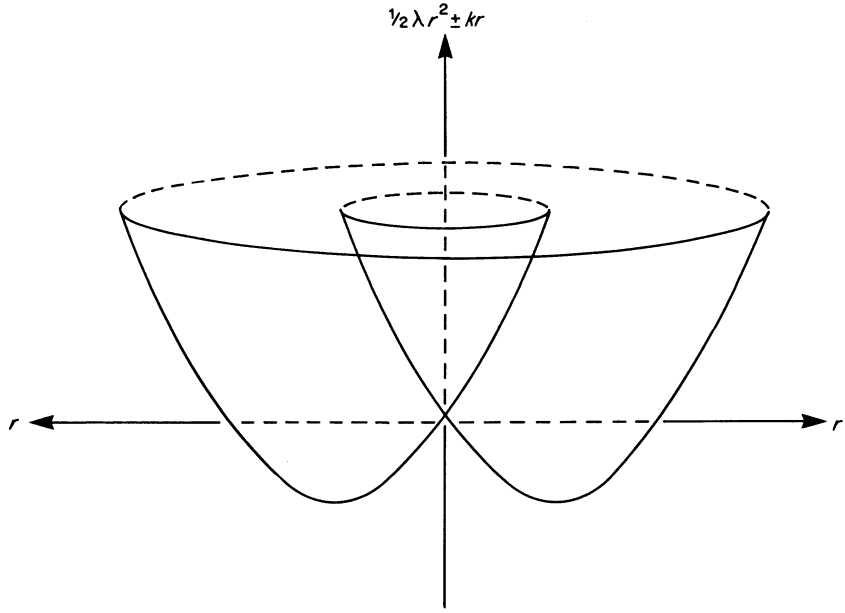


FIGURE 9. Potential energy diagram to show the Jahn–Teller splitting of orbitals of e symmetry in cyclopropane. Two branches result, $\frac{1}{2}\lambda r^2 \pm kr$, the depth of the well below the energy of the orbitals in the degenerate state being $\frac{1}{2}k^2/\lambda$. The magnitude of the distortion at the bottom of the well is given by $r = k/\lambda$[46]

M is the reduced mass and the motion of the molecule is characterized by a distortion parameter D (equation 9):

$$D = \frac{\text{depth of potential minimum}}{\text{zero point energy of vibration}} = \frac{k^2}{2\hbar}\sqrt{\frac{M}{\lambda^3}} \tag{9}$$

When D is small compared with unity the molecule oscillates about the central geometry but when D is greater than unity the molecule is strongly distorted most of the time.

The pattern of electron densities in Figure 2 leaves no doubt that the 3e′ orbitals are C–C bonding whilst the 1e″ are C–H bonding, the density lying out of the plane of the carbon atoms. Therefore it is to be expected that the orbitals labelled 3e′ are going to be much more susceptible to in-plane distortions such as depicted in Figure 8 than are those labelled 1e″, explaining why the results of the dynamic Jahn–Teller effect are more evident in the 3e′ than in the 1e″ case.

If $\psi_1, \psi_2 \ldots \psi_3$ are electronic orbital functions for a molecule with internal coordinates Q and Hamiltonian H then the potential energy surfaces of the molecule are eigenvalues of the matrix given in equation 10:

$$\begin{vmatrix} H_{11}(Q) - E & H_{12}(Q) \\ H_{21}(Q) & H_{22}(Q) - E \end{vmatrix} = 0 \tag{10}$$

The energies resulting from the above are given in equation 11.

$$E = \frac{H_{11} + H_{22}}{2} \pm \frac{\sqrt{(H_{11} - H_{22})^2 + 4H_{12}H_{21}}}{2} \tag{11}$$

In equation 10 it is explicit that $H_{11}(Q)$ etc. is dependent on Q; this is equally true in equation 11 where it is not made explicit but nevertheless $H_{11} \equiv H_{11}(Q)$, etc.

$$H_{12} = \langle \psi_1 | H | \psi_2 \rangle, \text{ etc.}$$

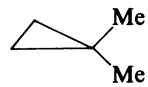
From equation 11, degeneracy of ψ_1 and ψ_2 is possible only if $H_{12} = H_{21} = 0$. Writing H as a power series in Q (equation 12)

$$H(Q) = H_0 + VQ + V'Q^2 + \ldots \tag{12}$$

and neglecting terms above the first order in Q it is found that $H_{12} = \langle \psi_1 | Q | \psi_2 \rangle = 0$ is the condition for degeneracy of ψ_1 and ψ_2. The above implies that $H_{12} \neq 0$ if Q transforms as one of the representations spanned by the direct product $\psi_1 \times \psi_2$ and for the D_{3h} group this means that vibrations of e′ symmetry alone are Jahn–Teller active.

Another molecule of D_{3h} symmetry (**4**) has a Jahn–Teller splitting of 0.49 eV (Figure 10) compared with 0.7 eV in cyclopropane. Such variations have been attributed to delocalization of the e′ orbitals[53]; differences in the distortion parameter of equation 9 no doubt play their part too. In **5** and **6** there are no degenerate orbitals and the spectra (Figure 11) are disarmingly similar; in **5** the first pair of bands is assigned to orbitals deriving from the 3e′ pair of the parent compound, i.e. cyclopropane, the splitting is 0.77 eV, but in **6** the band of lowest ionization energy derives from an orbital of predominantly C=C π character of cyclopropene and only the second band is assignable to an orbital deriving from 3e′ of cyclopropane. Hence it would be a mistake to equate the low energy pair of bands in the spectra of **5** and **6**.

(4)



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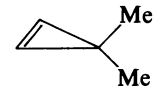


(6)

B. Effects of Conjugation

Suppose two groups, R and X, unite to form RX. If the orbitals of R and X have the same symmetry and overlap spatially they will mix and the conjugated system can be represented by equation 10a which is identical to equation 10 but is written in Hückel notation.

$$\begin{vmatrix} A_X - E & \beta \\ \beta & A_R - E \end{vmatrix} = 0 \tag{10a}$$

A_X is the Coulomb integral and β is the resonance integral[55]. Equation 13 derives from equation 10a in the same way that equation 11 derives from 10 and it shows that one effect of conjugation is to reduce the ionization energy of the uppermost occupied orbital, e.g. of X, by the amount $\Delta I(X)$.

$$\Delta I(X) = \frac{A_X - A_R}{2} - \frac{\sqrt{(A_X - A_R)^2 + 4\beta^2}}{2} \tag{13}$$

Some examples are given in Table 2 where it can be seen that the influence of the cyclopropyl group is the same in this respect as that of the vinyl group; as mentioned in Section II, this is also true as regards bond lengths.

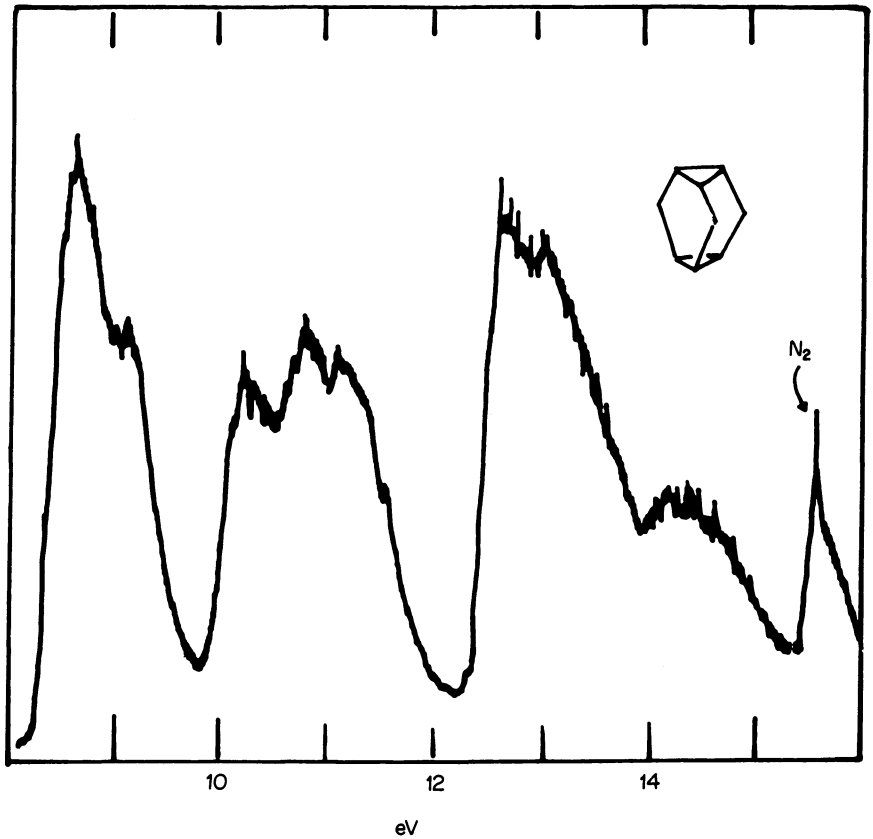


FIGURE 10. The He(I) photoelectron spectrum of **4**[52] which, like cyclopropane, has D_{3h} symmetry. A pair of bands at 8.67 and 9.16 eV are tentatively assigned to 7e′, the Jahn–Teller effect causing their separation from each other

It seemed natural to explain the cyclopropyl group's enhanced powers of conjugation (over other saturated alkyl groups) in terms of a supposedly large value of β thought to derive from the hybridization peculiar to the Walsh 3e′ orbitals (Figure 3) which consist of pure C(2p) atomic orbitals. However, Heilbronner and colleagues have pointed out that the β values are much the same for R = vinyl, methyl, isopropyl and cyclopropyl groups[29], lying between -1.9 and -2.4 eV, and instead of an explanation based on differences in hybridization[12] they draw attention to the quantity $A_R - A_X$ (equation 13) which differs substantially in the above series and in such a way as to confer a large value of ΔI on the cyclopropyl group. In fact ΔI is found to increase as $A_R - A_X$ falls in value and this fall arises from the high energies of the 3e′ orbitals of cyclopropane, in turn attributable to the low C–C–C bond angle (60° instead of 109.5°).

C. Effects of Spin-orbit Coupling

In alkyl and cycloalkyl bromides a complicating factor in the spectrum (Figures 12 and 13) is the presence of appreciable spin-orbit interaction which raises the degeneracy of

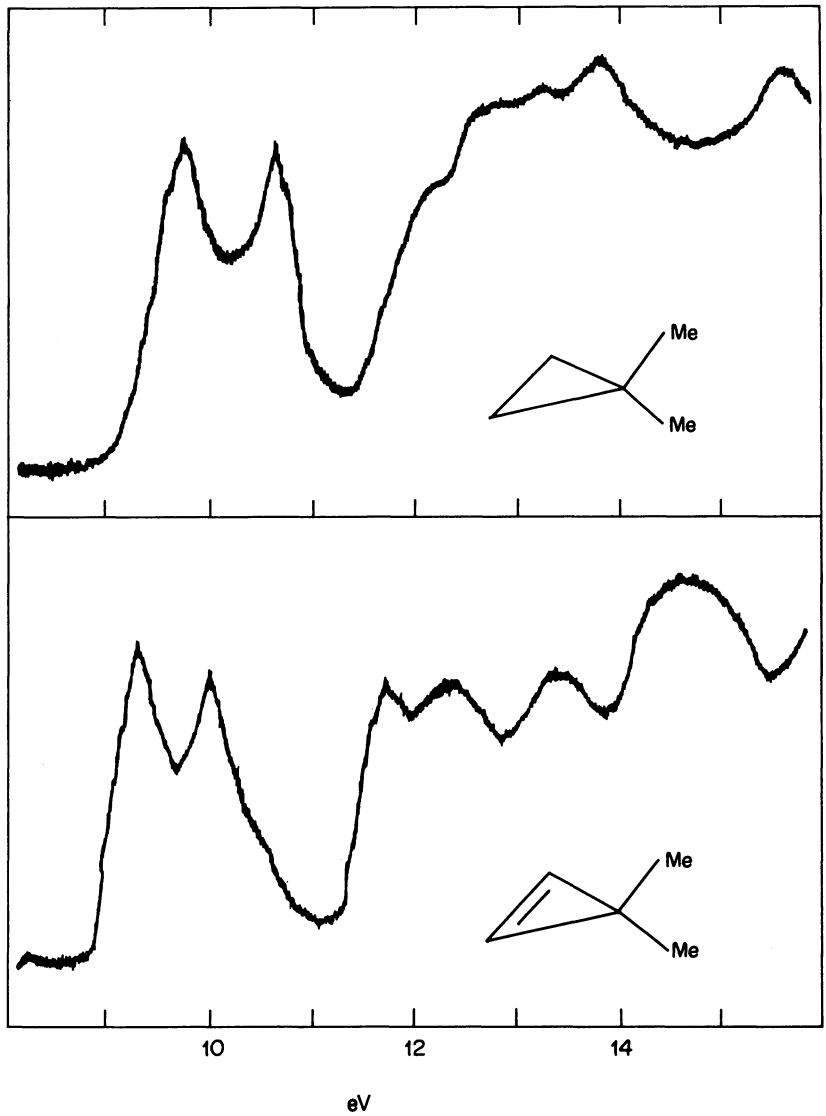


FIGURE 11. He(I) photoelectron spectra of cyclopropyl derivatives of C_{2v} symmetry[54]. The first pair of orbitals in 1,1-dimethylcyclopropane has vertical ionization energies of 9.8 and 10.57 eV, in the cyclopropene the energies are 9.42 and 10.02 eV; despite their similar appearance the first band derives in these pairs from orbitals of different type

certain orbitals (involving the halogen atom) that would appear from the ordinary three-dimensional character tables to be degenerate. The effect of spin-orbit interaction on the Hamiltonian is to introduce an extra term (equation 14) of the form $\xi \mathbf{l} \cdot \mathbf{s}$ where $\mathbf{l}$ and $\mathbf{s}$ are the orbital the spin angular momenta respectively and ξ is the spin-orbit coupling constant.

TABLE 2. The first vertical ionization energies (eV) for RX molecules consisting of two conjugated groups, R and X

XR	R = H	Me	i-Pr	*c*-Pr[a]	V[b]	Reference
H_2C=CH–R	10.5	9.7	9.5	9.2	9.2	28, 56
HC≡C–R	11.4	10.4	10.1	9.6	9.6	28
Br–R	11.7	10.5	10.1	9.9	9.8	20, 57

[a] Cyclopropyl.
[b] Vinyl.

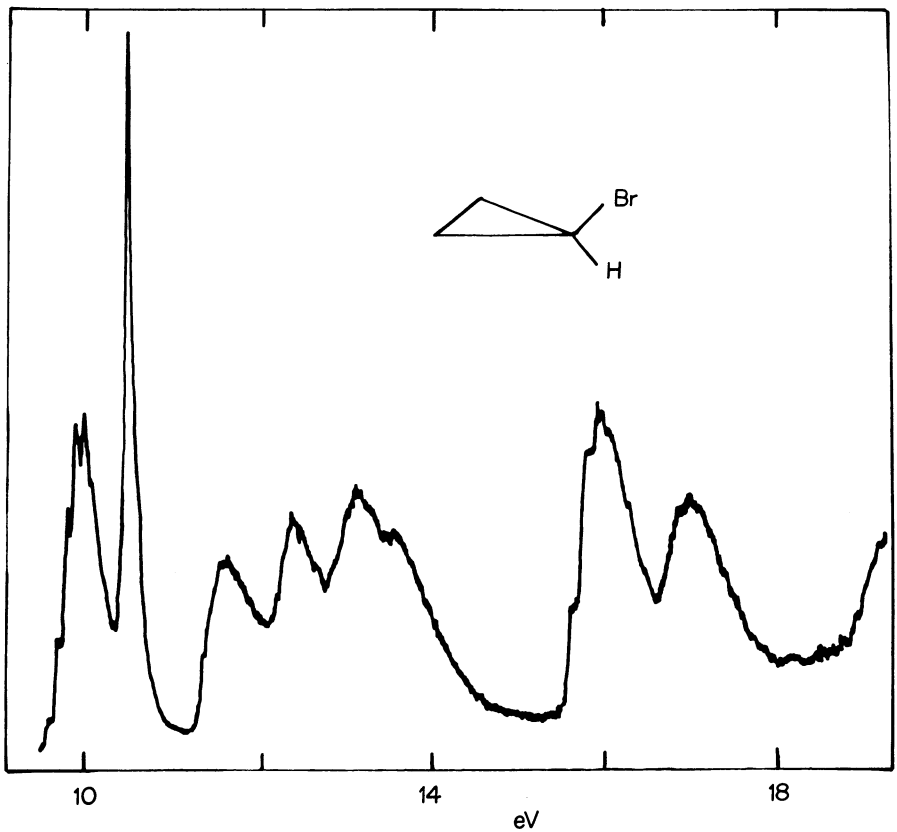


FIGURE 12. The He(I) photoelectron spectrum of cyclopropyl bromide[20]

The magnitude of ξ is roughly proportional in these systems to the square of the nuclear charge of the heavy atom[58].

$$H = H_0 + \xi 1 \cdot s \tag{14}$$

In equation 14 H_0 is the Hamiltonian appropriate in the absence of appreciable spin-orbit interaction. For Br (4p) atomic orbitals $\xi \simeq -0.31$ eV.

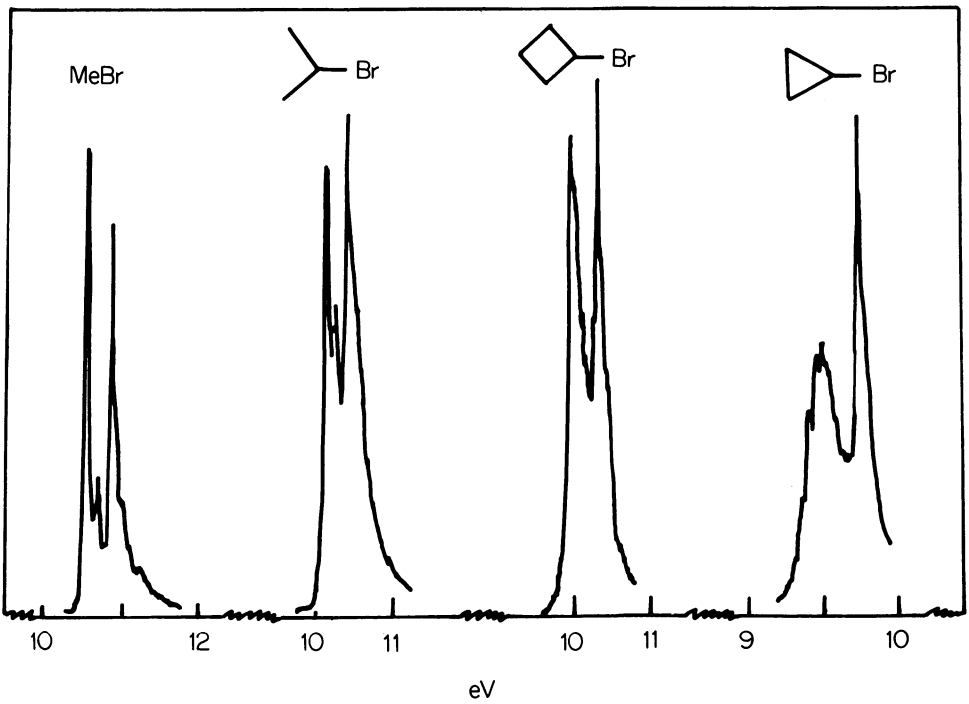


FIGURE 13. The bands of lowest energy in the He(I) photoelectron spectra of alkyl bromides, assigned to orbitals which are primarily Br(4p) in composition, split by spin-orbit coupling. Conjugation is shown up by the presence of vibrational structure, especially in the cyclopropyl compound[58]

The principles of calculation of the size of the spin-orbit interaction are straightforward in the case of a free atom or for truly localized atomic orbitals of atoms within molecules, e.g. the 4f orbitals in rare earth compounds. Thus Hund[59,60] accurately predicted values of the relevant moments L, J and S for rare earth ions in solid salts and aqueous solutions and showed that their magnetic moments were given by Van Vleck's equation[61] (equation 15):

$$\mu = \sqrt{4S(S+1)+J(J+1)} \tag{15}$$

However, for compounds of the iron group the magnetic moments are not given by equation 15 but by equation 16:

$$\mu = \sqrt{4S(S+1)} \tag{16}$$

and it was recognized long ago[62] that the loss of the J term was attributable to the 'quenching' of the orbital magnetic moment resulting from delocalization of the 3d orbitals over neighbouring atoms. In order that angular momentum can be quantized a certain degree of symmetry is required; in the free atom quantization about axes x, y and z is possible, in molecules of linear symmetry quantization about the linear axis is possible but in the point group C_{2v}, for example, no quantization is possible about any axis. Spin-orbit coupling, however, is an atomic effect and the symmetry of the atomic orbitals depends, as evidenced above, upon the degree to which they delocalize over the molecule in

which the atom finds itself. Hence the solution of the spin-orbit coupling problem in molecules involves not only the straightforward atomic terms deriving from equation 14.

Spin-orbit coupling and delocalization are in competition in a molecule like cyclopropyl bromide for two reasons:

1. in a delocalized orbital an electron spends less time in the magnetic environment of the heavy atom;
2. delocalization destroys the symmetry upon which the spin-orbit coupling effect depends.

Although 1. can be calculated readily[58,63–65], 2. presents difficulties although it is only one of a number of seemingly related phenomena, another example being the competition between spin-orbit coupling and the dynamic Jahn–Teller effect[66].

Assuming for a start that the local symmetry of the 4p orbitals of the bromine atom in cyclopropyl bromide is $C_{\infty v}$, with the p_x and p_y acting as non-bonding orbitals of π symmetry and p_z engaging in sigma bond formation, then angular momentum is quantized along the z axis, the operator being given by equation 17.

$$\hat{l} = \frac{\hbar}{i}\left(x\frac{\mathrm{d}}{\mathrm{d}y} - y\frac{\mathrm{d}}{\mathrm{d}x}\right) = \frac{\hbar}{i}\frac{\mathrm{d}}{\mathrm{d}\phi} \tag{17}$$

ϕ being the angle of rotation about the linear axis. The z-directed momentum is thus

$$\left\langle \psi \left| \frac{\hbar}{i}\frac{\mathrm{d}}{\mathrm{d}\phi} \right| \psi^* \right\rangle$$

the solutions being given by equation 18:

$$\psi_{\pm} = N\exp(\pm il\phi) \tag{18}$$

In equation 18 N is a normalization constant and l is the orbital momentum quantum number, equal to unity for p electrons; alternatively, therefore, equation 18 can be written in the form of equation 19:

$$\psi_{\pm} = \frac{l}{\sqrt{2}}(p_x \pm ip_y) \tag{19}$$

For the singly charged ion the possible spin functions are $|\alpha\rangle$ and $|\beta\rangle$ with the spin quantum numbers $\pm\frac{1}{2}$. Hence the total, space times spin quantum numbers can be denoted, in terms of the quantum numbers, $|1, \pm\frac{1}{2}\rangle$ and $|-1, \pm\frac{1}{2}\rangle$. The corresponding values of the total quantum number J are $1 \pm \frac{1}{2}$ giving the states $\Pi_{1/2}$ and $\Pi_{3/2}$. These states are assumed to be separated by ξ eV (equation 20):

$$\langle \pm 1, \pm\tfrac{1}{2}|\xi\hat{l}\cdot\hat{s}|\pm 1, \pm\tfrac{1}{2}\rangle = \pm\xi/2 \tag{20}$$

If one of the pair of π, 4p orbitals now interacts with a cyclopropyl orbital of 3e′ symmetry denoted $|\phi, \pm\frac{1}{2}\rangle$ such that equations 21 and 22 hold then the corresponding matrix is given by equation 23[63–65].

$$\langle p_x, \pm\tfrac{1}{2}|H|\phi, \pm\tfrac{1}{2}\rangle = \beta \tag{21}$$

$$\langle \pm 1, \pm\tfrac{1}{2}|H|\phi, \pm\tfrac{1}{2}\rangle = \beta/\sqrt{2} \tag{22}$$

$$\begin{array}{c} |1, \pm\frac{1}{2}\rangle \quad |-1, \pm\frac{1}{2}\rangle \quad |\phi, \pm\frac{1}{2}\rangle \\ \begin{vmatrix} A_X - E + \zeta/2 & 0 & \beta/\sqrt{2} \\ 0 & A_X - E - \zeta/2 & \beta/\sqrt{2} \\ \beta/\sqrt{2} & \beta/\sqrt{2} & A_R - E \end{vmatrix} = 0 \end{array} \tag{23}$$

Making the assumption that $A_X = A_R$ the solutions to equation 23 become those given in equation 24:

$$E = A_X, A_X \pm \sqrt{\xi^2/4 + \beta^2} \tag{24}$$

Solutions of equation 23 appropriate to the case of an alkyl bromide have been given[58], with values of β ranging from 0 to 1 eV and $\xi = 0.3$ eV, and it was found that the separation of the first pair of peaks is insensitive to the value of β in the range $\beta =$ 0–0.35 eV. This insensitivity could explain the constancy observed in the separation (Figure 13); alternatively some decrease in ξ with increasing β might be involved. That delocalization of one of the 'lone pair' Br(4p) orbitals has taken place in cyclopropyl bromide is evident from the vibrational fine structure and broadening of the first band in the spectrum[58]. In the C_s point group of the full molecular symmetry, the Br(4p) π orbitals span a′ and a″ (symmetric and antisymmetric with respect to the mirror plane) as do the 3e′ orbitals but the Br orbital of a′ symmetry is not expected to overlap its corresponding member on the cyclopropyl group very well—as a consequence the corresponding band remains sharp.

The He(I) photoelectron spectra of cyclopropylacetylene and cyclopropyl cyanide[2, 56, 67, 68] resemble that of the corresponding bromide (Figure 14); in these cases the π orbitals of the unsaturated groups replace those of the bromine atom and spin-orbit coupling is negligible.

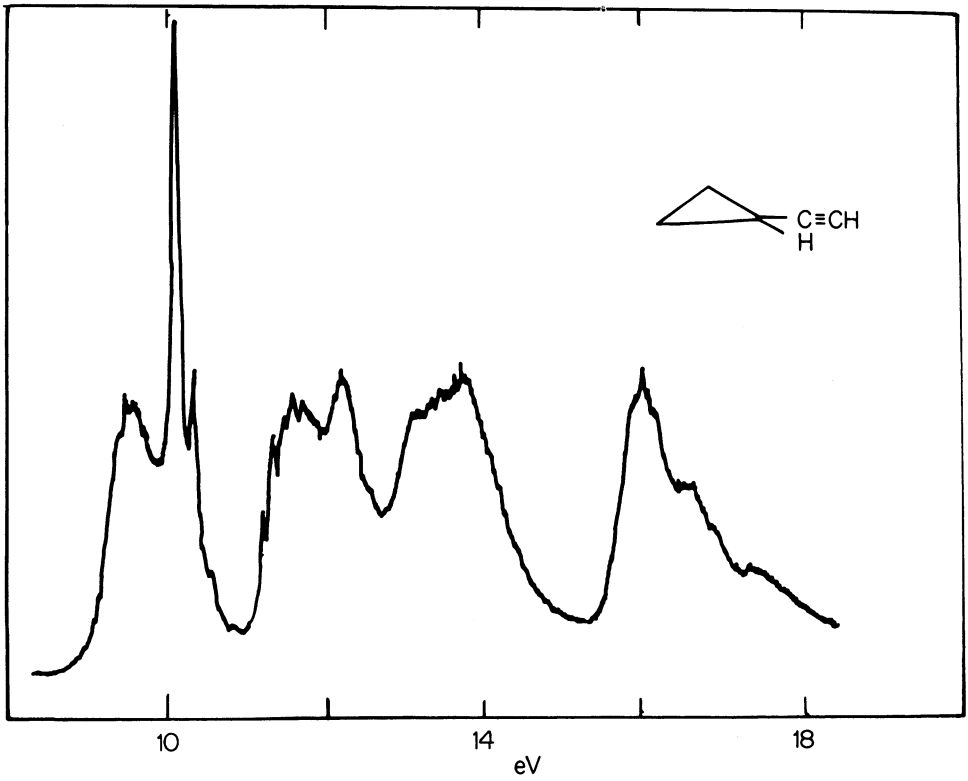
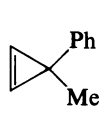


FIGURE 14. The He(I) photoelectron spectrum of cyclopropylacetylene[68]

D. Phenyl Derivatives

In the l-substituted-l-phenylcyclopropanes the upper pair of ionizations is assigned to the π levels of the aromatic ring and the next pair to the 3e′ levels of the cyclopropyl group; thus in Figure 15 the 3e′-derived bands are found in phenylcyclopropane at 11.11 and 10.53 eV (compared with 11.3 and 10.6 in cyclopropane) and at 10.6 and 10.1 eV in l-methyl-1-phenylcyclopropane (compared with 10.6 and 9.8 in methylcyclopropane). The splitting between the first pair of peaks in the spectra of these compounds remains unaltered upon the introduction of alkyl groups (even the *t*-butyl group) in the l-position[69] and all the evidence of photoelectron spectroscopy points to the conclusion that the barriers to rotation are small in these compounds. Further examples are given in Figures 16 and 17.



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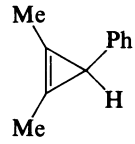

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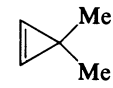


(9)

Again, in the spectrum of **7** (Figure 17) there appears to be no significant shift in energy of the bands of the constituent groups, at least in the threshold region. The first pair of bands in the spectrum of **7** is assigned to the phenyl group, the second to the cyclopropene group. The first pair of bands in compound **9** lie at 9.42 and 10.02 eV, in **7** they are found at 9.66 and 10.49 eV, the 9.66 band being assigned to the ethylenic π orbital and the 10.49 band to a modified 3e′ orbital of cyclopropane. It is reported[71] that the replacement of the methyl group in **7** by hydrogen in **8** lowers the ionization energy of the lowest band from 8.49 to 8.17 eV.

E. Cyclopropyl Amine

The so-called 'lone pair' orbital of nitrogen generally has the lowest ionization energy in an alkyl amine and cyclopropyl amine is no exception, the corresponding band (numbered 1 in Figure 18) having a vertical ionization energy of 9.41 eV. Conjugation between one of the 3e′ orbitals of the cyclopropyl ring and the lone pair has been suggested[20] with the result that some sigma C–C character exists in the nominally lone pair orbital and some N lone pair character exists in the third orbital to be ionized, the second remaining close to its original cyclopropyl 3e′ character. Bands 4 and 5 are assigned to orbitals derived from the 1e″ orbitals of the ring but they are better resolved than in the spectrum of cyclopropane itself (Figure 6) on account of the involvement of one of these orbitals with the C–N bond, the other having a node at the substituted carbon atom (see Figure 2); SCF calculations suggest that the orbital corresponding to band 4 is restricted largely to the cyclopropyl group whilst that for band 5 contains the sigma C–N character[20]. The succeeding bands, 6 and 7, also seem to relate directly to the corresponding bands of cyclopropane.

F. Methylenecyclopropane

The first band in the spectrum of methylenecyclopropane (Figure 19) is assigned to the ionization of the C=C π orbital of $2b_1$ symmetry (Figure 20). Bands 2 and 3 are due to the ionization of the $4b_2$ and $8a_1$ orbitals respectively (equivalent to 3e′ in cyclopropane). The fourth band is attributed[20] to the $1a_2$ orbital (derived from the cyclopropane 1e″) and the fifth to $3b_2$, a C–H bonding orbital.

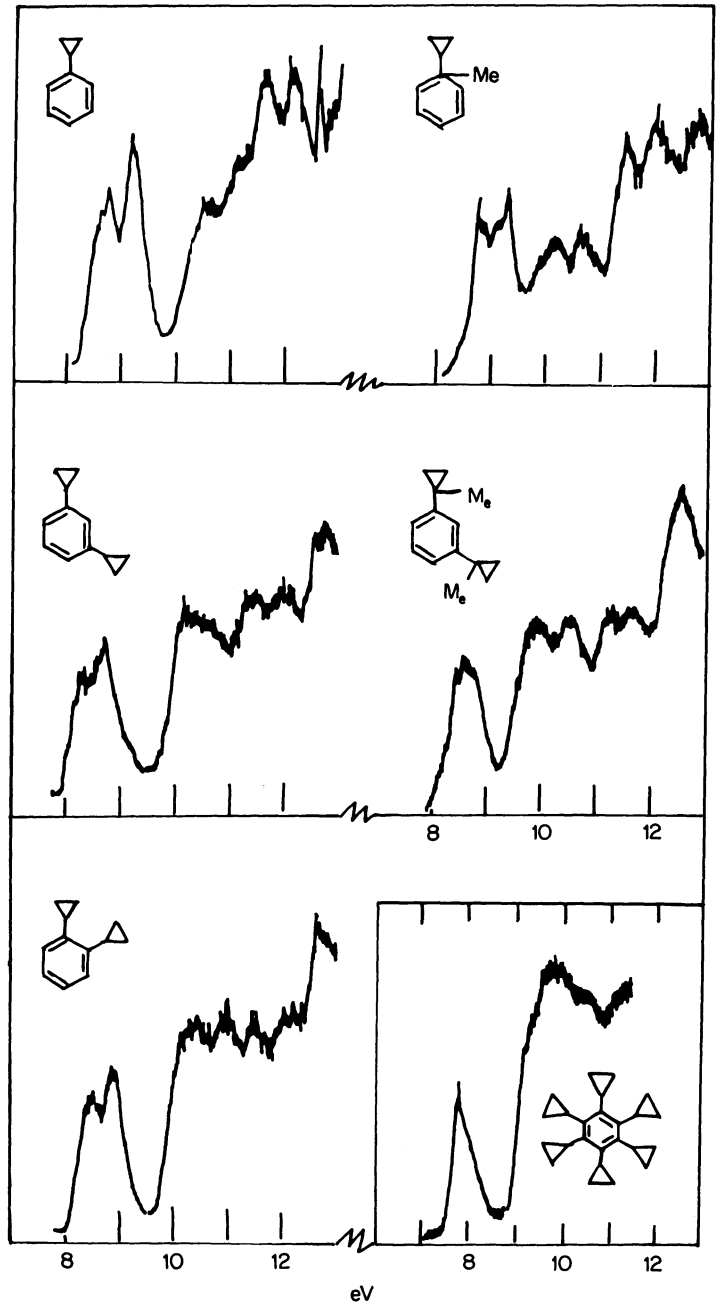


FIGURE 15. He(I) photoelectron spectra of some phenyl derivatives of cyclopropane[70]

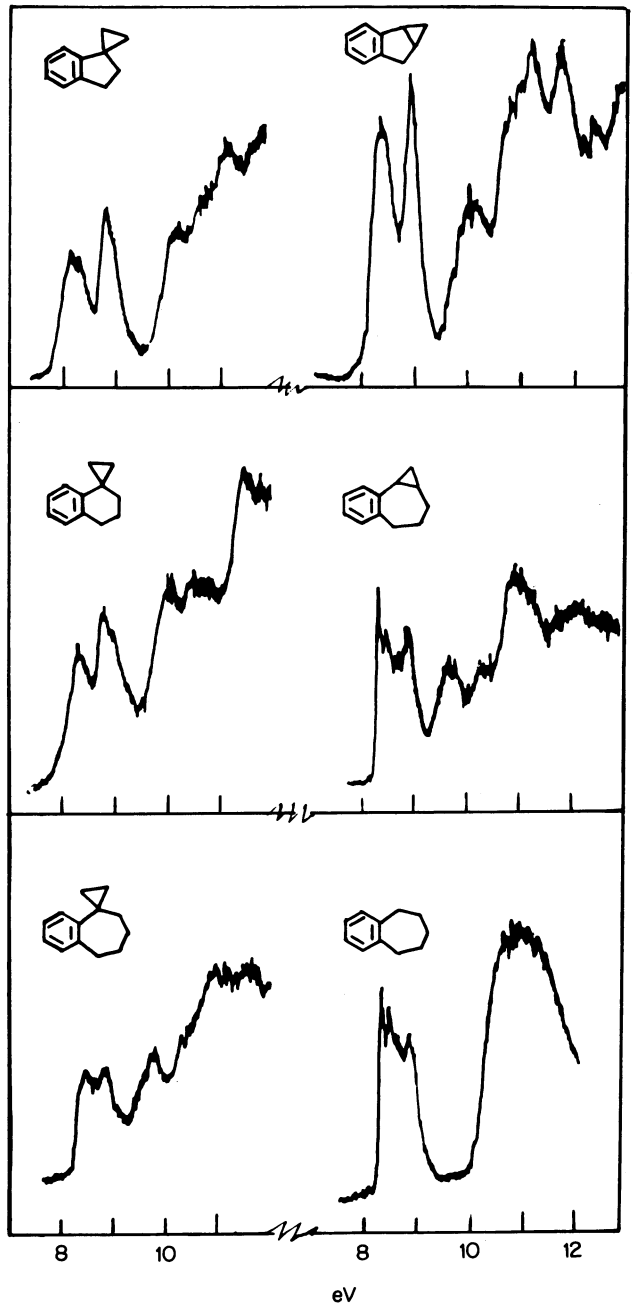


FIGURE 16. He(I) photoelectron spectra of some phenyl derivatives of cyclopropane[70]

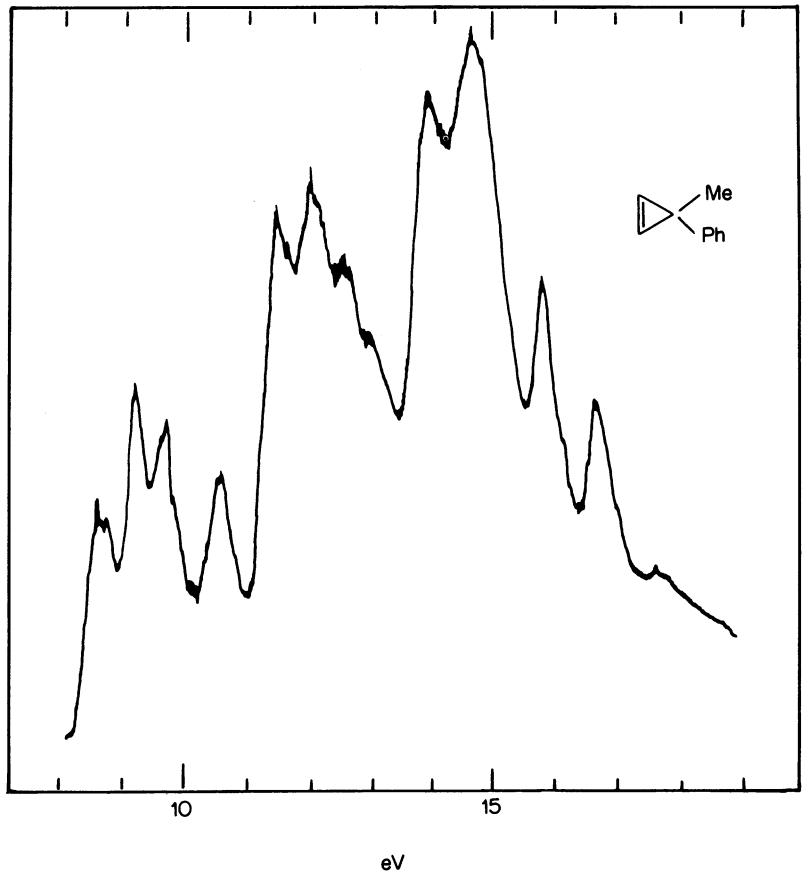


FIGURE 17. He(I) photoelectron spectrum of 3-methyl-3-phenylcyclopropene (7)[71]

G. Cyclopropyl Rings with Shared Edges

The ionization sequence in tetrahedrane is expected to be determined by its tetrahedral symmetry in which orbitals of e and t_2 character are liable to give bands structured by the influence of the Jahn–Teller effect. So far only the tetra-t-butyl derivative is known (Figure 21) and the spectrum contains prominently at about 8 eV two bands separated by about 0.7 eV which have been assigned to the 1e orbital of the ring system[73], above 10 eV the spectrum is dominated by bands loosely describable as deriving from ionizations of the flexible t-butyl groups. In the T_d point group the degeneracy of the e representation is raised by vibrations of e character which lower the symmetry to D_{2d} (an epikernel) and to D_2 (the kernel). The t_2 representation is similarly subject to the dynamic Jahn–Teller effect in virtue of both e and t_2 vibrations but in this case either three bands are expected or two of unequal intensity, hence the observed pair of peaks of equal intensity is consistent with the above assignment.

The spectrum of bicyclobutane is discussed in Section IV.

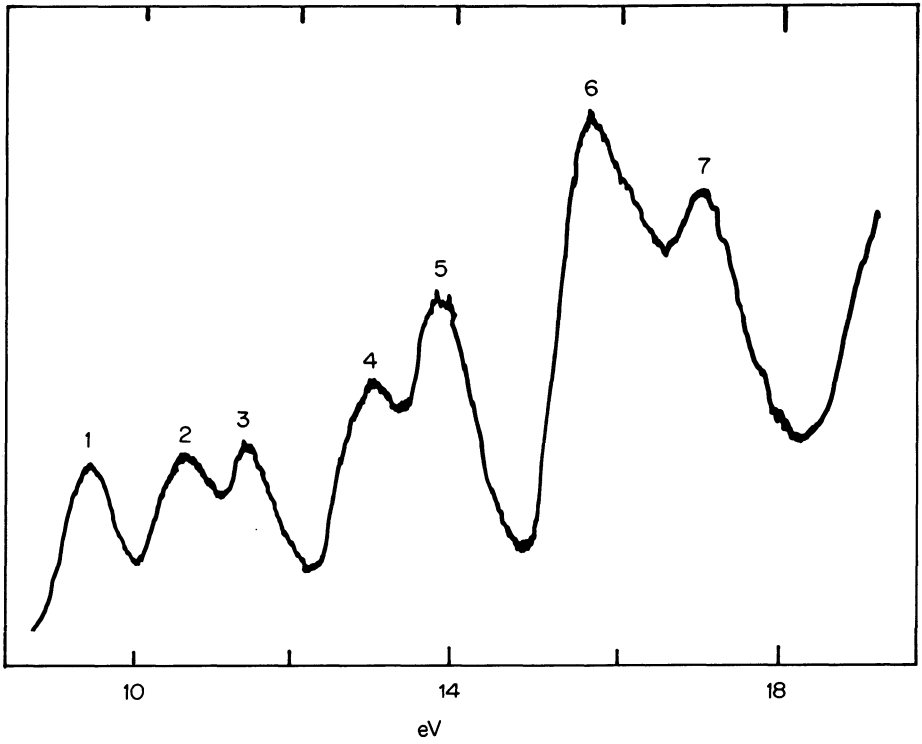


FIGURE 18. The He(I) photoelectron spectrum of cyclopropyl amine[20]

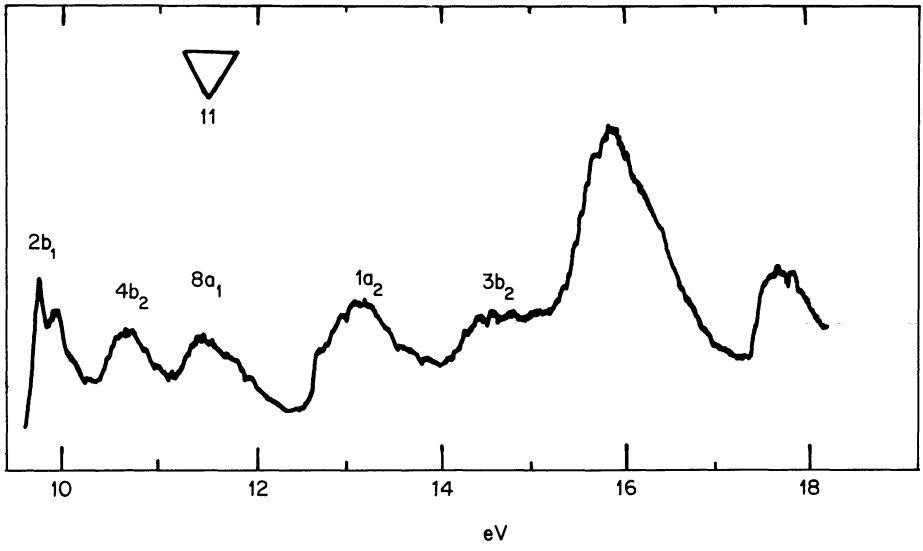


FIGURE 19. The He(I) photoelectron spectrum of methylenecyclopropane[20]

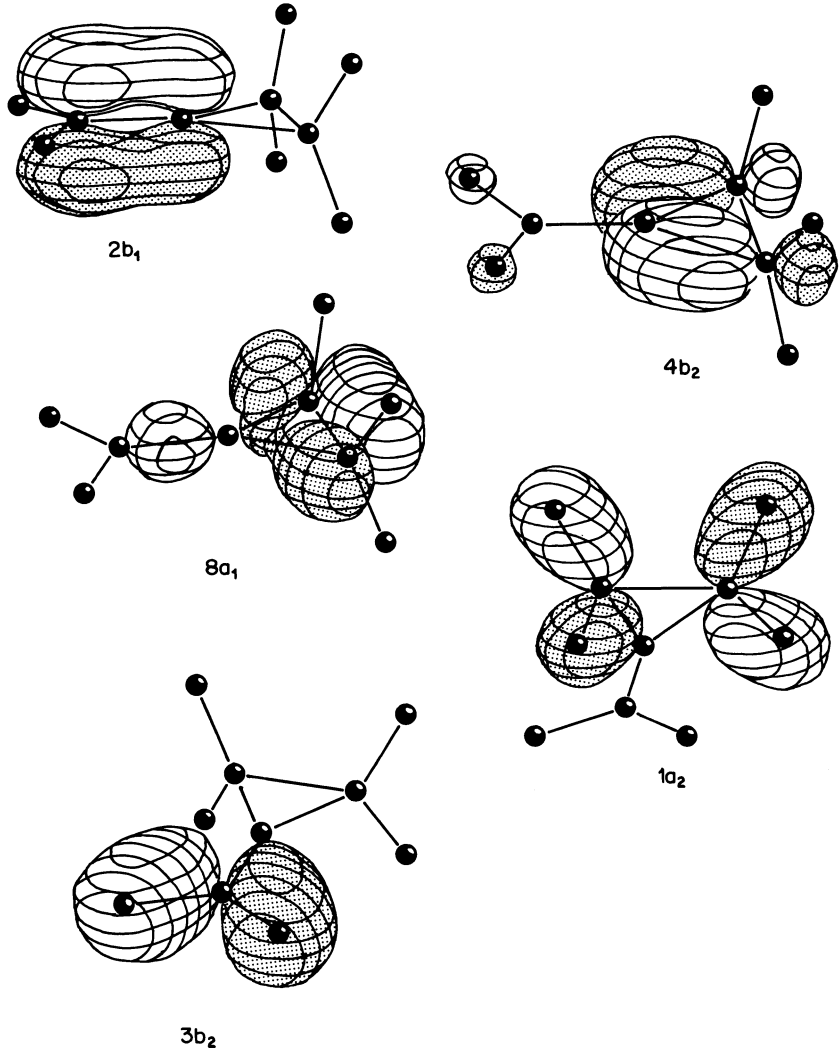


FIGURE 20. Electron density surface contours for the occupied orbitals of methylencyclopropane derived from an SCF calculation[21]. The figures are in order of energy, the highest at the top

The well resolved spectrum of benzvalene is given in Figure 22, see also Table 3. The first orbital to be ionized, $4b_2$, derives from the ethylene π orbital and is therefore not found in the spectra of **10** and **11** (Table 3); the second, $10a_1$, correlates closely with the $7a_1$ orbital of bicyclobutane (Section IV) being substantially unaltered by the introduction of the ethylene group in benzvalene[20].

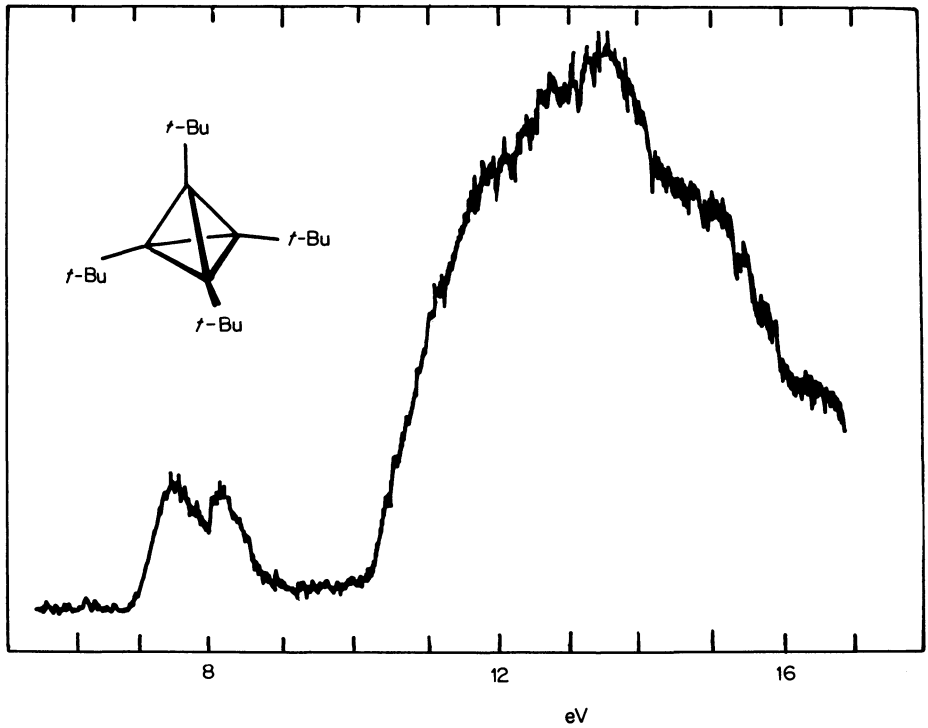
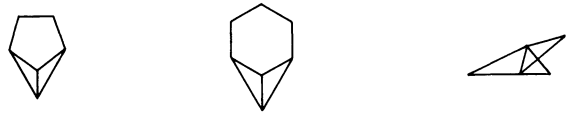


FIGURE 21. The He(I) photoelectron spectrum of tetra-*t*-butyltetrahedrane. The twin peaks of low intensity at threshold are assigned to the 1e orbitals of the rings split by the dynamic Jahn–Teller effect. Bands of higher energy are overlapped by ionizations of the *t*-butyl groups

The spectrum of the [1.1.1] propellane **12** has been measured by Heilbronner and colleagues[72] (Figure 23) but the interpretation is not yet available.



(10) **(11)** **(12)**

III. CYCLOPROPENE

The correlation diagram (Figure 24) shows how the molecular orbitals of cyclopropene relate to those of cyclopropane. The uppermost of the occupied orbitals of cyclopropene ($2b_1$) is predominantly of C=C π bond character (Figure 25) and has no counterpart in cyclopropane; the corresponding band (Figure 26) has a short vibrational progression of

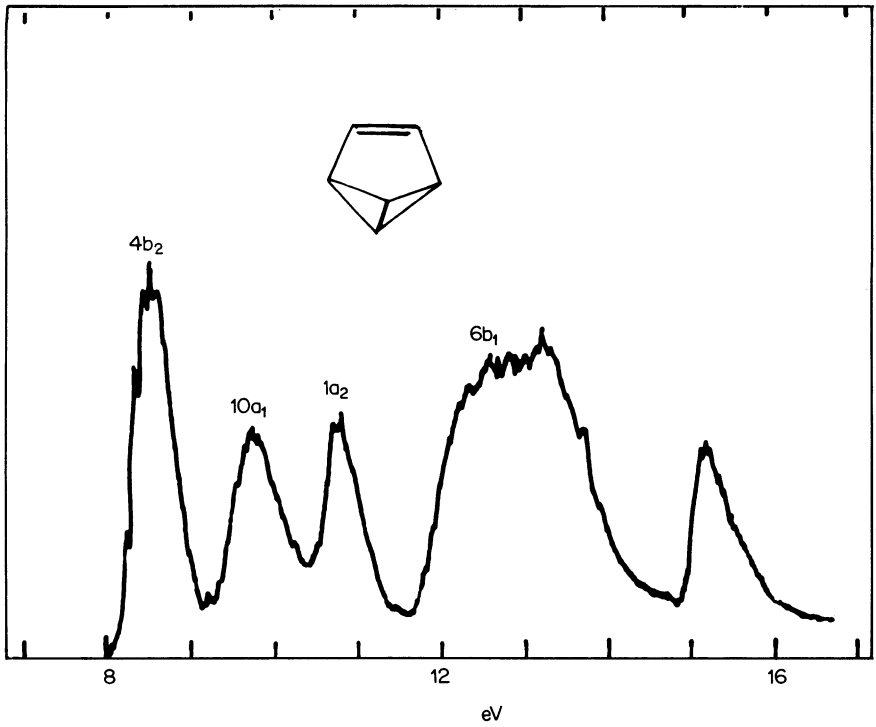


FIGURE 22. The He(I) photoelectron spectrum of benzvalene[74]

TABLE 3. Ionization energies and assignments of bands in the He(I) photoelectron spectra of the indicated compounds[74]

Band	Benzvalene	10	11
1	8.55 ($4b_2$)	9.43 ($10a_1$)	8.72 ($12a_1$)
2	9.75 ($10a_1$)	10.23 ($2a_2$)	10.45 ($2a_2$)
3	10.83 ($1a_2$)	11.53 ($4b_2$)	10.8 ($5b_2$)
4	12.18 ($6b_1$)		

Energies in eV.

positive anharmonicity, the frequency being consistent with the assignment of C=C stretch (ground state frequency $\nu = 1656\ cm^{-1}$).

It is to be noticed in Figure 26 that the intensity decreases after the $5a_1$ ionization; that this was to be attributed to configuration interaction was mentioned in Section I.

A. Cyclopropenone

The first band in the spectrum of cyclopropenone (Figure 27) is assigned to the $4b_2$ orbital (Figure 28) which is a combination in about equal proportions of the carbonyl 'lone

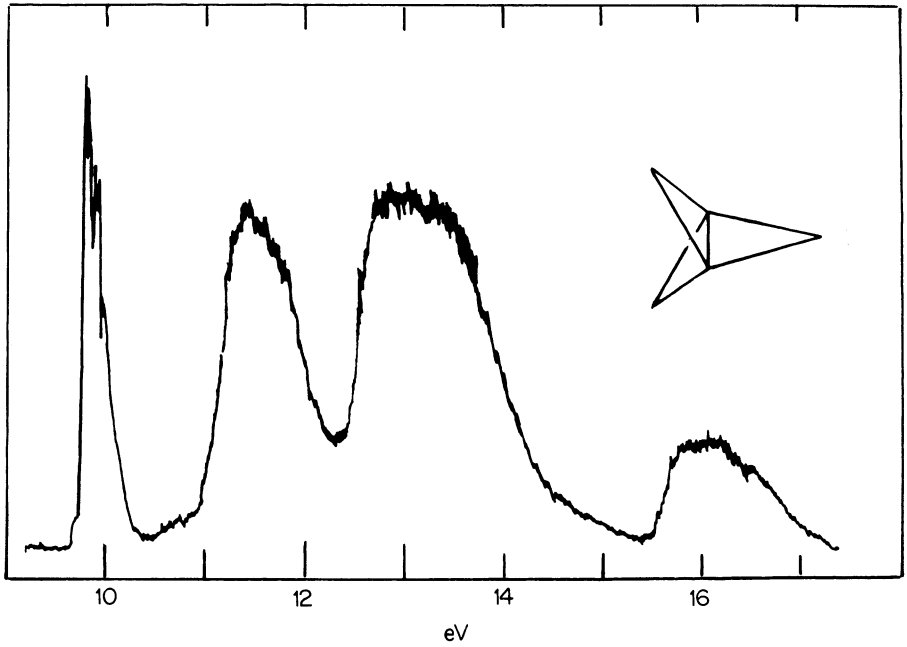


FIGURE 23. The He(I) spectrum of [1.1.1]propellane[72]

pair' and the $3b_2$ orbital of cyclopropene (Figure 25)[76]. The vibrational progression of the first band has a frequency of 820 cm^{-1} and has been assigned speculatively to the C–C stretching vibration of frequency 1043 cm^{-1} in the neutral molecule.

The second band is allocated to the $2b_1$ orbital which is another mixture in equal proportions of the C=C π orbital of cyclopropene (Figure 25) and the C=O π orbital; there is a small component only of the carbonyl carbon atom's orbitals in this molecular orbital[76]. There is a vibrational progression on the second band attributed to C=C bond stretching vibrations having the frequency 1380 cm^{-1} compared with 1467 cm^{-1} for the neutral molecule. The decrease in frequency is here much less for the C=C stretching vibration than it is in cyclopropene itself on account of the reduced π overlap in the C=C bond. The only other vibrational progression, on the $7a_1$ band, is again assigned to C=C stretch and has the frequency 1370 cm^{-1}.

IV. PHOTOELECTRON/PHOTOION COINCIDENCE MEASUREMENTS

The principles of photoelectron/photoion spectroscopy were given in Section I and an example is given in Figure 29 which shows the He(I) photoelectron spectrum of bicyclobutane and beneath it the coincidence spectra of those fragment ions formed in appreciable quantity by the relaxation of the ions produced by the photoelectric effect. This type of spectroscopy gives directly the mass/charge ratio of the ionic fragments resulting from the dissociation of an ion in a precise energetic state, the internal energy of the ion being simply the difference between the ionization energy of the state concerned

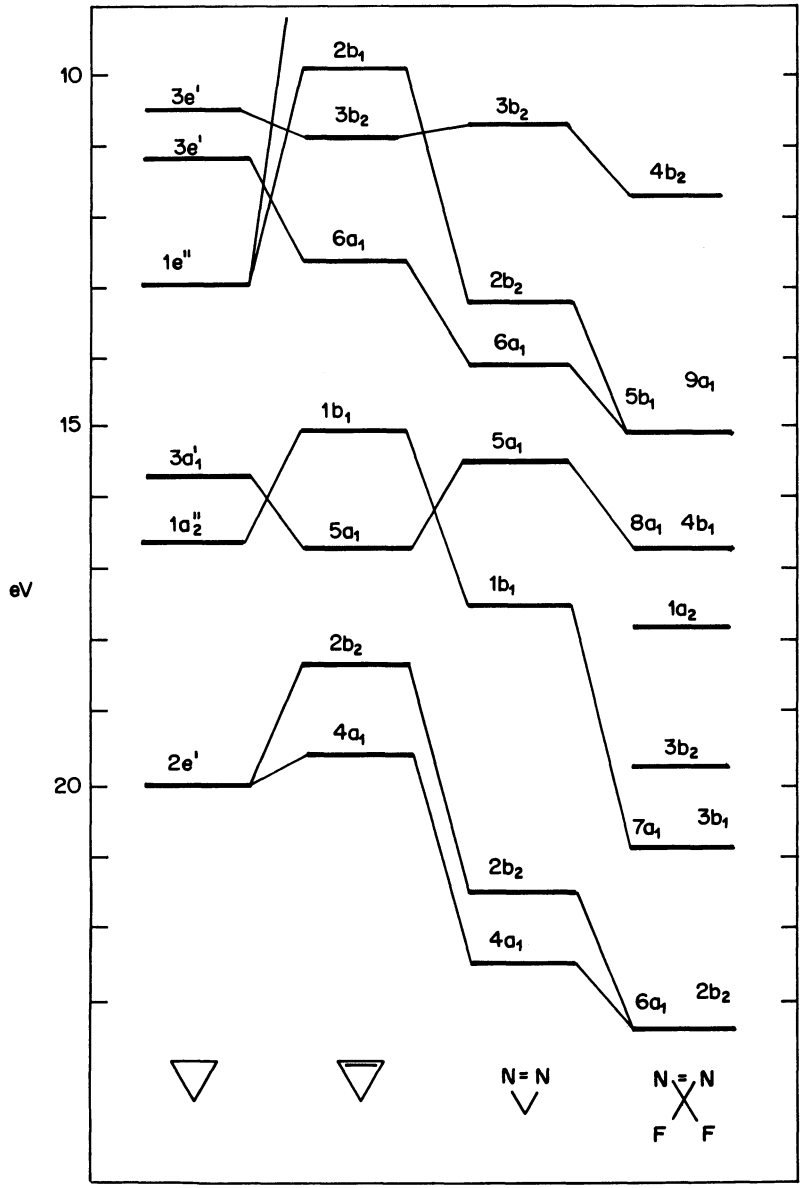


FIGURE 24. Correlation of observed photoelectron peaks according to SCF calculations[75]

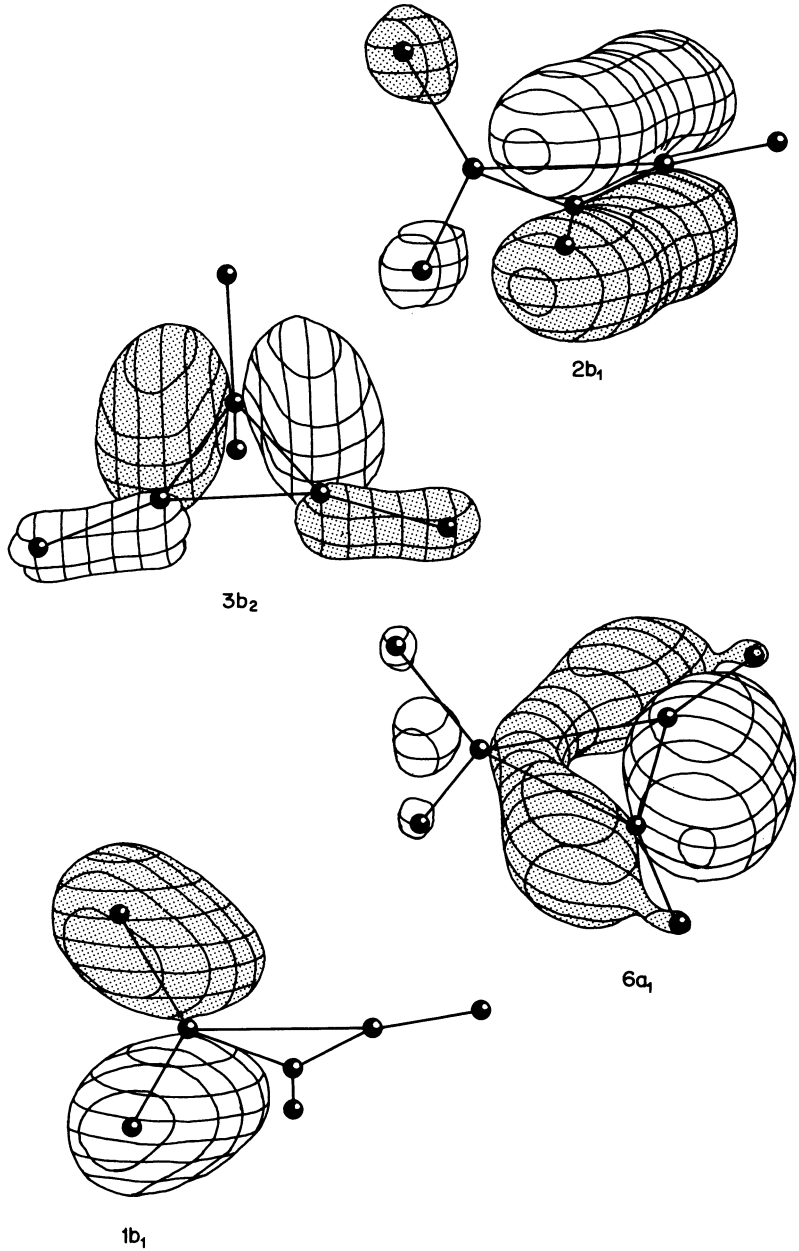


FIGURE 25. Electron density contours for the occupied orbitals of cyclopropene derived from an SCF calculation. The individual figures are in order of energy, the highest at the top[21]

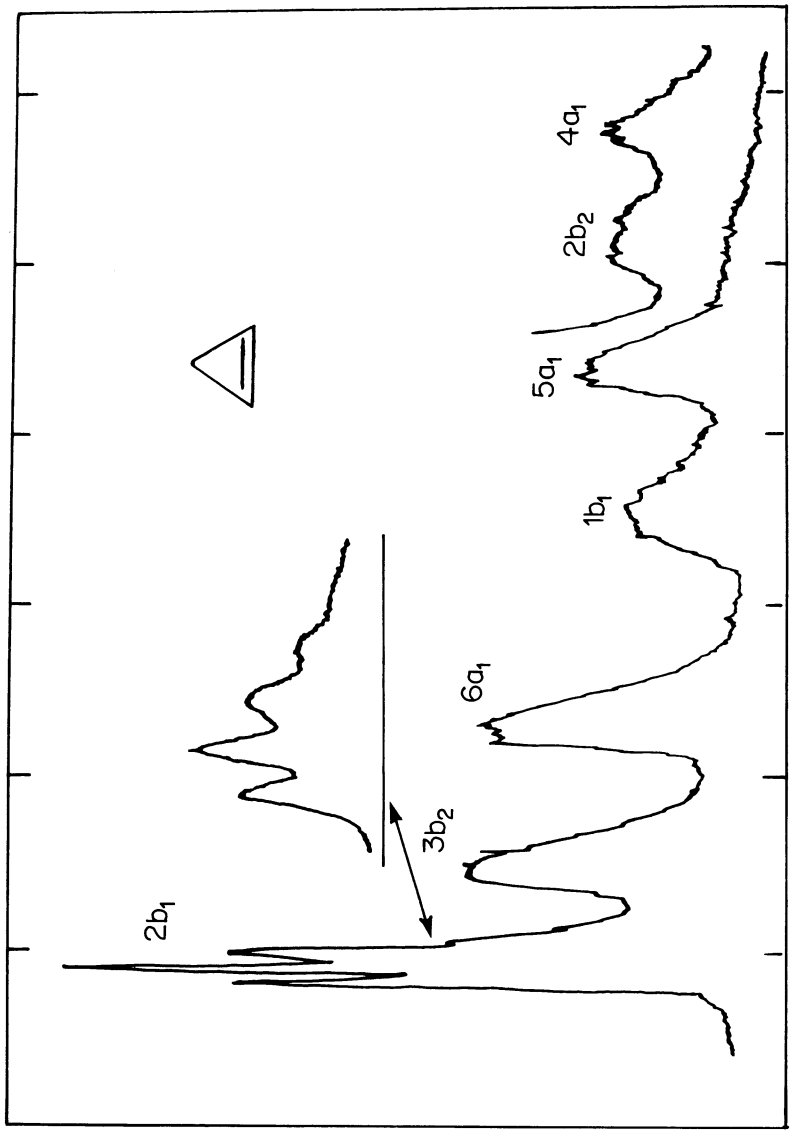


FIGURE 26. The He(I) photoelectron spectrum of cyclopropene[75]. Inset, the vibrational progression of the first band has positive anharmonicity and is probably due to the C=C stretching vibrations

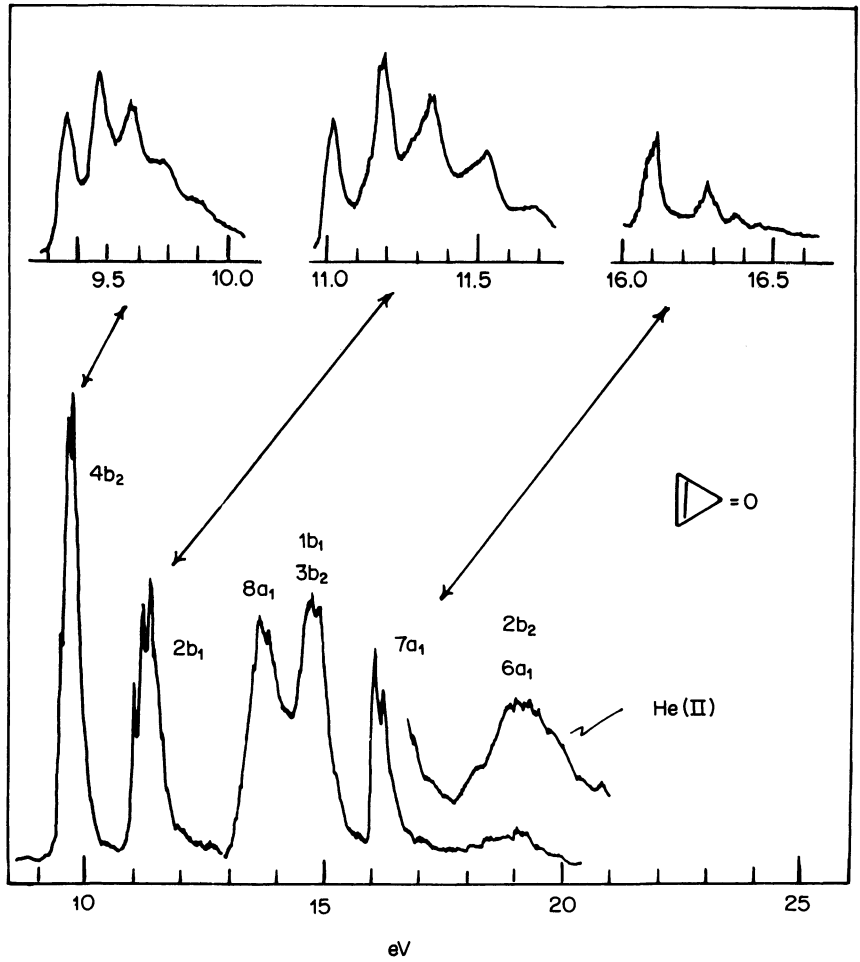


FIGURE 27. The photoelectron spectrum of cyclopropenone[76] showing the He(I) and a fragment of the He(II) result

and the threshold ionization energy. It is assumed that the internal energy is rapidly degraded and distributed over the various degrees of freedom of the ground state of the ion which then goes on to isomerize, to dissociate or first to isomerize and then to dissociate.

The well resolved spectrum of bicyclobutane is assigned to the various orbitals in Figure 29, the first orbital to be ionized, $7a_1$, being of π bonding character and localized across the transannular C–C bond (Figure 30). Below an ionization energy of about 10 eV, He(I) radiation does not cause appreciable fragmentation of bicyclobutane, i.e. the ground state of the ion formed by the ionization of the $7a_1$ orbital is stable to dissociation except, as can be seen in Figure 29, for those ions of high vibrational excitation formed at the extreme edge of the $7a_1$ band which give a small amount of $C_3H_3^+$ (presumably in the form of cyclopropenium cation) and a little $C_4H_5^+$.

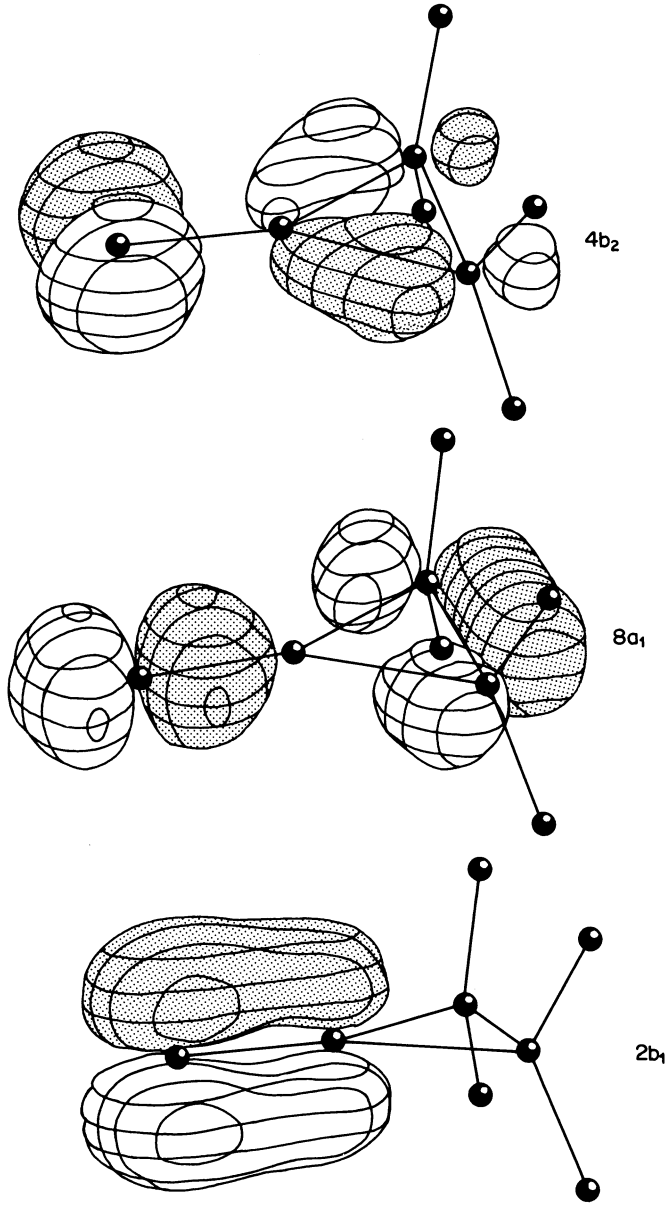


FIGURE 28. Electron density contours for cyclopropenone derived from an SCF calculation. The individual figures are in order of energy, the highest at the top[21]

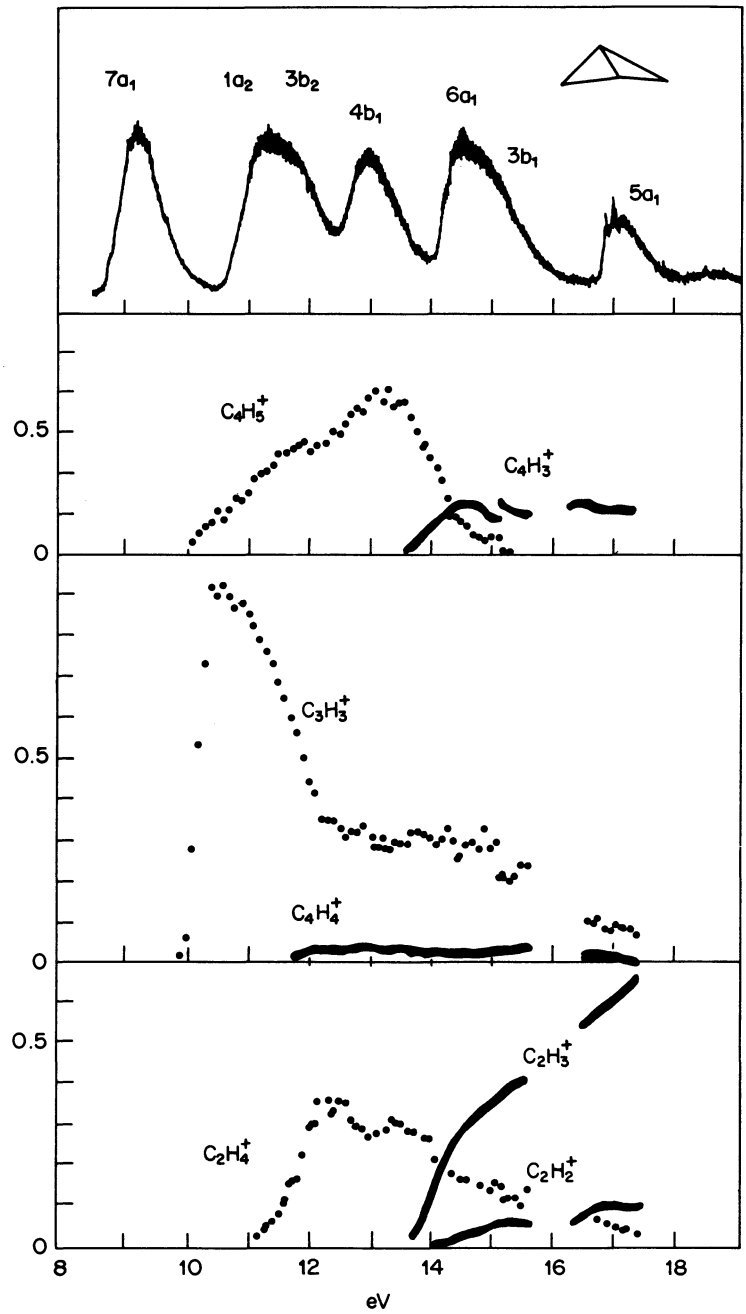


FIGURE 29. He(I) photoelectron spectrum of bicyclobutane (upper figure) and the photoelectron/photoion coincidence spectra of various fragment ions showing their yields on the scale 0 to 1.0. No measurements were possible around $I = 16$ eV on account of the low intensity of the photocurrent there[4]

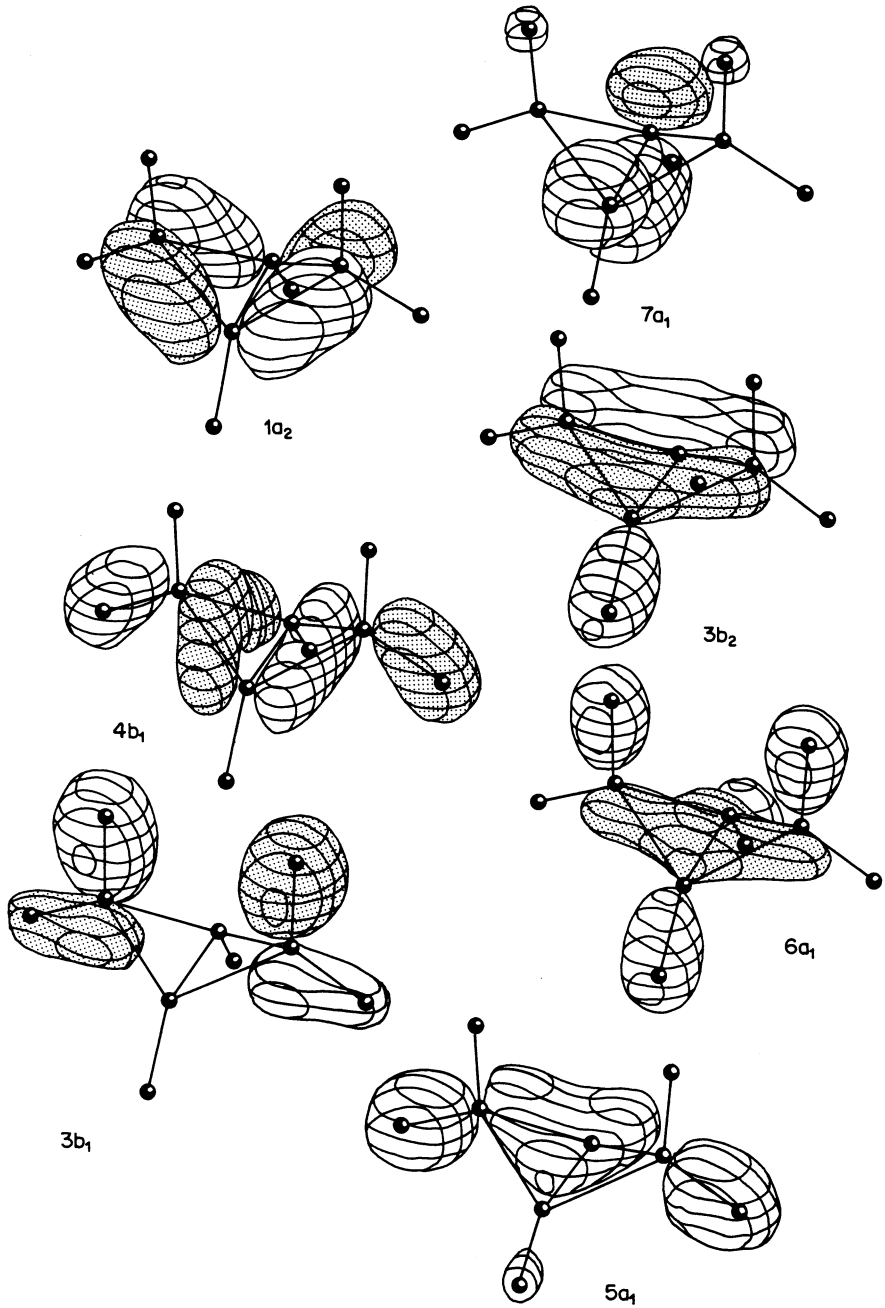


FIGURE 30. Electron density surface contours for the occupied orbitals of bicyclobutane derived from an SCF calculation[21]. The individual figures are in order of energy, the highest at the top

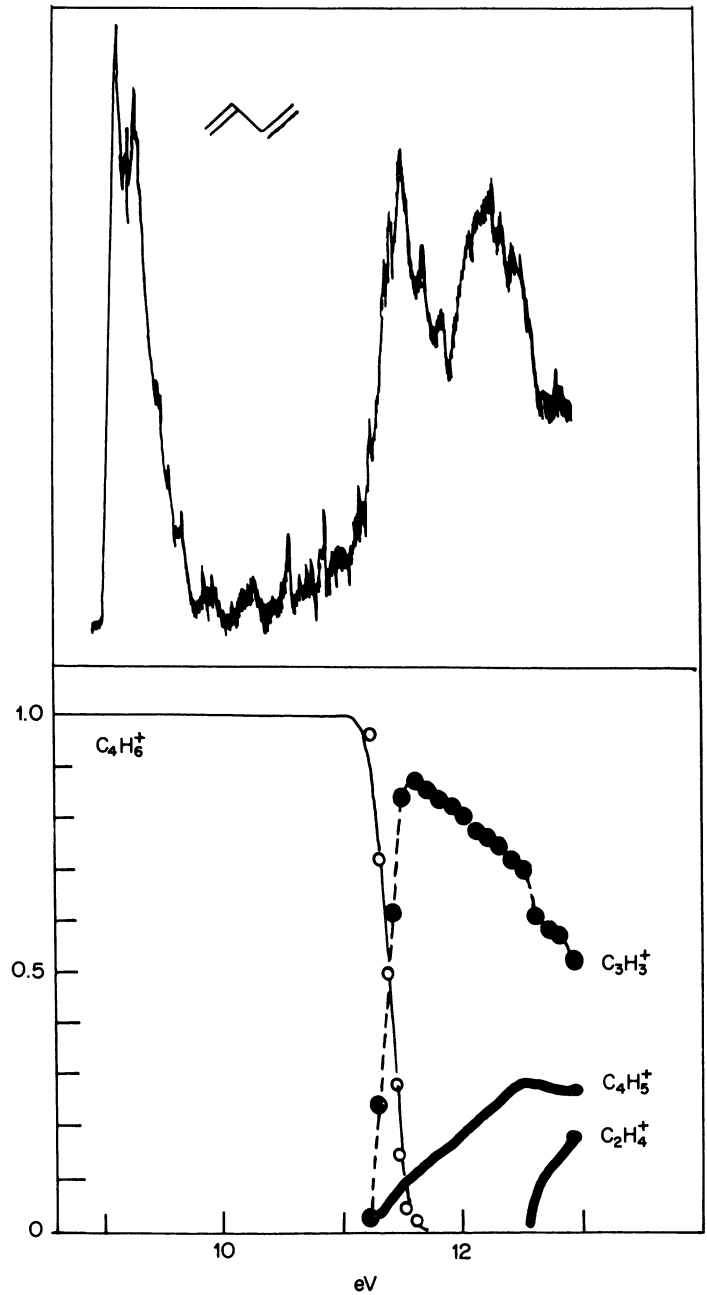


FIGURE 31. He(I) photoelectron spectrum of 1,3-butadiene (upper figure) and photoelectron/photoion coincidence spectra of various fragment ions. The yield of ion is indicated on the scale 0 to 1.0[80]

From the measurement of the time of flight of the cations their dissociation rates can be calculated and, using statistical theory, it was possible to conclude[4] that the unimolecular rate constant for dissociation (of the order of 10^3 s^{-1} at I = 10–10.5 eV) was too small by a factor of 10^3 for the possibility that the bicyclobutane cation itself could be the immediate precursor of the fragments. The results were suggestive that a complete isomerization to the cation of 1,3-butadiene occurs before dissociation.

The dominant process in the fragmentation of various isomers of $C_4H_6^+$ is

$$C_4H_6^+ = C_3H_3^+ + Me$$

The same mass spectrum was found when the isomers 1,3-butadiene, cyclobutene, 1-butyne, 1,2-butadiene, 3-methylcyclopropene, etc. were ionized by electron bombardment and Vestal[77] pointed out the implication that the threshold energy of isomerization was less than that for fragmentation. From the mass spectroscopy of D-labelled 1-butyne it was shown[78] that complete scrambling of the hydrogen atoms occurred at low internal energies whilst an increase in internal energy coincided with an increase in the probability of the loss of a methyl group. More recent mass spectroscopic studies have extended these findings: in 1,3-butadiene cation, hydrogen atom randomization was found to be complete in about 10^{-11} s; carbon atom randomization was slower. At low internal energies the loss of a methyl group was slower than carbon atom randomization but at high internal energies it was faster[79].

In Figure 31 the photoelectron/photoion coincidence curves for 1,3-butadiene are shown, the branching ratio (ion yield) is much larger for $C_3H_3^+$ than for any other fragment, as originally noted by Vestal, and since the cyclopropenium cation is stabilized by resonance, obeying the $4n+2$ rule with $n = 0$, it is a major product in many cases. Photoelectron/photoion coincidence experiments with 1,2-butadiene, 1,3-butadiene, 1-butyne, 2-butyne, cyclobutene and 3-methylcyclopropene[81,82] have shown that isomerization proceeds before the formation of $C_3H_3^+$ and the other products when the internal energies are of the order of a few eV.

$C_3H_3^+$ is also the major product in the breakdown of the cations of allene[83], propyne and cyclopropene[84] and all these isomers have similar photoelectron/photoion coincidence spectra, consistent with the assumption of isomerization to a common intermediate before dissociation. The preceding remarks apply also to the C_6H_6 isomers: benzene, 2,4-hexadiyne and 1,5-hexadiyne where $C_3H_3^+$ is accompanied by $C_6H_4^+$ and $C_4H_4^+$ among the fragmentation products which are identical in these cases[85]. Again, in the C_4H_5N isomers pyrrole, methacrylonitrile, allyl cyanide and cyclopropyl cyanide[86], fragmentation occurs via a common precursor, possibly the cation of pyrrole; in this case the most abundant product is $C_2H_3N^+$, possibly the linear keteneimine, $CH_2=C=NH$.

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CHAPTER **6**

Acidity and basicity of cyclopropanes

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I. INTRODUCTION

The two most fundamental properties affecting the chemical reactivity of cyclopropane and its derivatives are the subject of this chapter. The only previous review treating both topics, acidity and basicity of cyclopropanes, appears to be that of Charton[1] in an earlier volume of this series, *The Chemistry of Alkenes*, Volume 2. In effect, the present review may be considered a detailed critical update of developments in these two related areas. Literature coverage is not intended to be complete and apologies are extended to those authors whose work of topical importance may not have been included. While there is some variability between sections, the literature surveyed is inclusive to June, 1985.

An attempt has been made to extend the discussion to the unsaturated derivatives of cyclopropane, i.e cyclopropene and methylenecyclopropane; however, the treatment is not extensive either due to a paucity of pertinent chemistry or to coverage elsewhere in this volume (Cyclopropenes, Chapter 21; Cyclopropenyl derivatives, Chapter 24). The reader will also note that the discussion on basicity of cyclopropanes is considerably more extensive due to the wealth of new chemistry and conceptualizations in the past dozen or so years.

II. BONDING CONSIDERATIONS

There are two classical approaches to bonding in cyclopropane[1], namely the Walsh molecular orbital approach and the bent bonds or banana bonds of the Coulson–Moffit model.

The Walsh molecular orbitals[2-7] of the cyclopropane skeleton (Figure 1) resulting from overlap of three sp^2 orbitals and three p orbitals include two cyclic arrays of orbitals, an outer Möbius array[8] (3e's and $1a_2'$) and an inner Hückel array of sp^2 orbitals ($2a^1$ and 4e'). In ground state cyclopropane, of the Hückel orbitals which make up the σ-framework of the molecule only the bonding 2a' orbital is populated and this orbital corresponds to a closed three-center, two-electron bond. The array is aromatic but electron deficient. The orbitals of the Möbius cyclic array form the π-framework of cyclopropane. The bonding *anti*-symmetric Möbius orbital (3e') and its degenerate symmetric orbital form the bonding π system of cyclopropane, and contain between them four electrons, making this array aromatic and electron rich.

The interaction of the bent banana bonds[9] of the classical Coulson–Moffit valence bond model of cyclopropane which uses methane-like sp^3 hybrids and joins three units to form the alicyclic ring imply a resonance energy in cyclopropane of 69 kcal mol^{-1} [10]. Modern molecular orbital calculations (STO-3G) support an electron rich π system and an electron deficient σ-system for cyclopropane.

The comparability of both conventional strain energy[11] based on an experimentally measured enthalpy of formation and an enthalpy of formation for a hypothetical strainless–CH_2–increment of cyclopropane (28.3 kcal mol^{-1}) and cyclobutane (27.4 kcal mol^{-1}), and the activation energy[12] required to effect rupture to 1,3- and 1,4-diradicals respectively (Δ, 64.2 kcal mol^{-1}: $\square$, 62.5 kcal mol^{-1}) belies the difference in angle strain energy[10] (Δ, 74.4 kcal mol^{-1}: $\square$, 15.4 kcal mol^{-1}) between these two strained cyclic systems. This comparability in conventional strain energy and activation energy for homolytic bond rupture requires compensatory stabilization of cyclopropane and/or destabilization of cyclobutane. Dewar estimates[10] a σ-aromatic stabilization of cyclopropane of 55.1 kcal mol^{-1} compared with a localized bond model. This stabilization is substantially greater than the resonance energy stabilization of benzene. Cyclobutane would exhibit σ-*anti*-aromaticity being the σ-conjugated analog of cyclooctatetraene and its conventional strain energy may be partly due to σ-*anti*-aromatic character. This effect in the larger four-membered ring is expected to be small since the *anti*-aromatic energy of

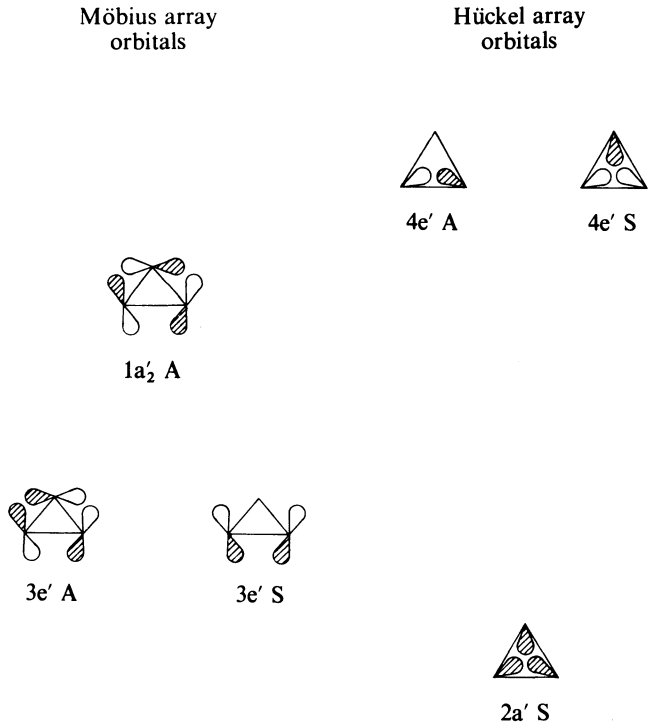


FIGURE 1. Walsh molecular orbitals of cyclopropane

cyclooctatetraene is only 3 kcal mol^{-1}. It is perhaps notable that the carbon–carbon bond length of cyclobutane[13] (1.548 Å) is greater than that in cyclopropane[14] (1.509 Å). Cyclobutane therefore behaves differently from cyclopropane since the strain energy per methylene in cyclobutane is only one-fifth that in cyclopropane and not three-quarters as would be estimated from a consideration of only conventional strain energy data in the absence of compensatory σ-aromaticity[10].

The greater facility of cyclopropane compared with cyclobutane to undergo ring-opening with electrophiles and exhibit conjugation to a π system or carbocation center is generally considered to result from relative weakening of the σ-bonds in cyclopropane by angle strain thereby allowing for greater interaction with electrophiles or an adjacent π system[10]. The energy of activation for protonation of cyclobutane has been calculated to be considerably greater than for cyclopropane[15]. Protonated cyclobutane is calculated to have relatively long bond lengths to the protonated carbon such that the species can be regarded as a methyl cation associated with the edge of a cyclopropane ring.

The carbon–carbon σ-bonding orbitals for cyclopropene are analogous to those for cyclopropane with, of course, superpositions of the π_{cc}-bonding orbital $(2B_1)^7$ representing the HOMO. Similar considerations hold for the ring orbitals of methylenecyclopropane.[7] Again, hybridization effects and ring strain provide for unique chemistry for these three-membered ring systems compared to their unsaturated cyclobutane and larger ring analogs.

III. ACIDITY

A. General Aspects

The measurement of acidities of weak carbon acids in non-aqueous solvents is fraught with difficulties such as ion-pairing phenomena, differential solvation, etc[16]. Despite these problems, as long as a link could be established with the aqueous pK_a scale, sufficiently consistent results were obtained so that by 1965 Cram was able to establish the MSAD scale of carbon acidities[17], summarizing the work of McEwen, Streitwieser, Applequist and Dessy. In order to extend the pK_a range much above 35, the kinetic acidities of the carbon acids must be determined using the isotope exchange method. Relation to the thermodynamic pK is established using the Brønsted catalysis law ($\alpha = 0.31$ for conjugated anions and $\alpha = 0.9$ for localized anions[17]). Streitwieser[18–25] has been a major proponent of the exchange method working in cyclohexylamine as solvent with cesium cyclohexylamide (CsCHA) or lithium cyclohexylamide (LiCHA) as base catalyst. Table 1 lists some useful values of pK_as of weak carbon acids determined by this approach.

TABLE 1. pK_a values (approximate) for some weak carbon acids

Hydrocarbon	Exchange method (Streitwieser *et al.*)	Electrochemical method (Breslow *et al.*)
Methane	48[21]	58 ± 5[28]
Ethylene	44[22]	46[28]
Propene (allylic H)	43 ± 1[25]	47–48[28]
Cyclopropane	46[19]	—
Cyclopropene (allylic H)	—	61[26]
1,2,3-Trimethylcyclopropene (ring H)	—	74[26]
1,2,3-Triphenylcyclopropene (allylic H)	—	50[26]
Cyclobutane	50[19]	—
Cyclopentane	51[19]	—
Cyclohexane	52[20]	—
Isobutane	—	71[27]
Benzene	43[23]	—
Toluene	41.2[24]	44–45[28]

An alternative approach to pK_a determination for very weak hydrocarbon acids is the electrochemical method of Breslow[26–28]. This method is thermodynamic in origin employing voltammetric reduction/oxidation of the cation (or anion) to radical thence to anion (or cation) and comparing the energetics of these steps to the triphenylmethyl system (including bond dissociation energies of the respective hydrocarbons). Values of pK_as obtained for some weak carbon acids by this method are given in Table 1 for comparison with the Streitwieser results.

Comparison of the two sets of pK_a values for the hydrocarbons ethylene, propene, and toluene demonstrates fair agreement between the two methods although the values obtained by application of the thermodynamic cycle are consistently 3–4 units higher. On the other hand, Breslow's estimate of the acidity plateau for saturated hydrocarbons (methane[28], isobutane[27]) in the pK range of 60–70 seems intuitively reasonable. If this view is correct then the Streitwieser values for methane and the cycloalkanes, including cyclopropane, are likely to be 5–10 pK units too low, although the relative ordering of these extremely weak acids is probably correct. These conclusions are reasonable if it is assumed that isotope exchange does not proceed through a fully developed carbanion[17].

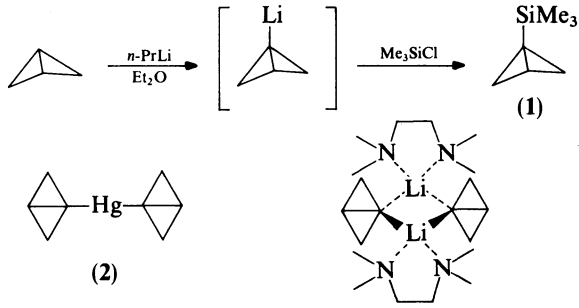
B. Cyclopropane and Related Strained Hydrocarbons

On the basis of the above analysis a more reasonable estimate of the pK_a of cyclopropane would be about 51 ± 5. Elevation of the pK_a to this level places the acidity of cyclopropane in better perspective. Thus, although the accepted Walsh and valence bond (bent bond) bonding schemes assign nominal sp^2 character to the exocyclic carbon bonds of cyclopropane and this is supported by the ^{13}C–H coupling value (161 Hz) a cyclopropane C–H is several orders of magnitude less acidic than a vinyl C–H or benzene C–H. Nevertheless, cyclopropane is, relatively, more acidic than the other saturated cycloalkanes and within this narrow series Streitwieser and coworkers[19] have demonstrated a linear correlation of $J(^{13}C\text{–H})$ values for $c\text{-}C_3 - c\text{-}C_6$ with the respective logarithms of the rate constants for isotopic exchange.

Although the relationship between acidity and carbon–hydrogen coupling constants is a useful predictive tool, strict adherence is inappropriate as is obvious from the ethylene: cyclopropane comparison. A less obvious case in point is the relative acidities of cubane and cyclopropane. Despite its lower ^{13}C–H coupling constant (155 Hz) cubane undergoes base-catalyzed isotope exchange some 10^3 times more rapidly than cyclopropane[29]. The reasons for this discrepancy remained obscure for a time; however, a recent study of the correlation of ^{13}C–H coupling constants with the sum of valence bond distortions in saturated hydrocarbons[30] suggests that the source of the problem may be in the observed coupling constants. By use of an empirically derived relationship, cubane was identified as having an anomalously low $^1J_{CH}$ (155 Hz as compared with a calculated value of 164 Hz) whereas cyclopropane's $^1J_{CH}$ was unusually high (161 Hz as compared with a calculated value of 152 Hz). In this case at least, kinetic acidities may be a better measure of the relative amounts of s character in C–H bonds.

On the other hand, Luh and Stock[29] argued that the increased acidity of cubane could be rationalized by significant rehybridization at the bridgehead carbon with enhancement of the percent s character in the lone pair orbital. Very recently, more than ten years after the appearance of the original publication, theoretical calculations have been published[31] supporting this position. Normally, non-stabilized carbanions are expected to exhibit nearly the same structure and carbon hybridization as the respective carbon acids[17]. Thus, cyclopropane and the cyclopropyl anion are shown[31] to have essentially the same geometry by virtue of the fact that percent s character of the anion orbital, 32%, is the same, nominally, as the s character in the corresponding C–H bond. By contrast, the cubyl anion's bridgehead orbital is calculated to experience a 21% increase in s character, to 52% from the estimated 31% for the bridgehead C–H (evaluated using $\%s = {}^1J_{CH} \times 0.2$). Presumably, the driving force for altered hybridization of the cubyl anion is diminished internal strain in the three adjacent C–C bonds. While these theoretical results appear to be qualitatively reasonable, they will require verification before the magnitude of the exaltation of s character can be accepted.

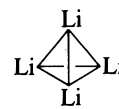
Annelation of a second small ring to an edge bond of cyclopropane results in increased bond angle strain at, predominantly, the bridgehead carbons and, accordingly, increased s character in the exocyclic bridgehead carbon orbitals. Thus, for bicyclo[1.1.0]butane the observed[32] bridgehead $^1J_{CH}$ of 205 Hz suggests 41% s character for the exocyclic bridgehead carbon orbital. From a plot of percent s character vs. pK_a, established using the values for methane, ethylene and cyclopropane in Table 1 plus the pK_a for acetylene (25.0)[33], the pK_a for the bridgehead C–H of bicyclobutane may be estimated to be in the range of 35–37, or at least ten pK units more acidic than a cyclopropane C–H. This enhanced acidity has been put to synthetic use with the synthesis of 1-trimethylsilylbicyclo[1.1.0]butane (**1**)[34] and bisbicyclobutylmercury (**2**)[35]. Indeed a stable crystalline complex of 1-lithiobicyclo[1.1.0]butane and TMEDA has been isolated and shown to have the dimeric structure (**3**) by X-ray analysis[35].



Various bridged bicyclobutane analogs have been synthesized and the acidity of their bridgehead hydrogens exemplified by kinetic or synthetic means. A partial listing would include the following systems: tricyclo[4.1.0.0^{2,7}]heptane (**4**)[36,37]; tricyclo[3.1.0.0^{2,6}]hexane (dihydrobenzvalene) (**5**)[36,38]; tricyclo[2.1.0.0^{2,5}]pentane (**6**)[36]; and benzvalene (**7**)[39].

4; $n = 3$ **6**; $n = 1$
5; $n = 2$ **8**; $n = 0$

(7)

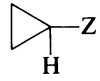
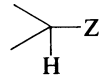


(9)

Although the ultimate bridged bicyclobutane system, tetrahedrane (**8**), has resisted synthetic efforts to date, its tetralithio derivative (**9**) is claimed[40] to be a product of low temperature (−45°C) photolysis of dilithioacetylene in liquid ammonia. Calculations suggest that the most stable structure of tetralithiotetrahedrane should have a lithium cation centered at each of the four faces of the tetraanion rather than at the corners as indicated by structure (**9**).

C. Substituent Effects on Cyclopropyl Anion Structure and Stability

In view of the enhanced acidity of protons attached to a cyclopropane ring, it might have been expected that conjugating groups Z would increase the acidity of the methine proton in **10** at least to the same extent as for the similar proton in the isopropyl model system (**11**). The discovery[41,42] that nitrocyclopropanes (e.g. **10d**) are generally weaker Brønsted acids than their homologous and acyclic counterparts provided the first indication of the invalidity of this assumption. Despite a conflicting earlier report[43] for benzoylcyclopropane (**10c**)[44], determination of the base-catalyzed isotopic-exchange rates for a series of cyclopropyl ketones, including **10c**, established a similar reluctance to enolate formation at the cyclopropyl α-carbon[44,45]. Similar conclusions[46,47] have been reached for cyclopropane carboxylic acids and esters (**10f**). On the other hand, kinetic evidence has accumulated to suggest that the cyano[45,48] and arylsulfonyl derivatives[45,49,50] of cyclopropane, i.e. **10g** and **10e**, are somewhat more acidic than their acyclic analogs (**11g**) and (**11e**).

(10) **(11)**

a, Z = $CH{=}CH_2$, **b**, Z = Ph; **c**, Z = COPh; **d**, Z = NO_2
e, Z = SO_2Ph; **f**, Z = CO_2R; **g**, Z = CN; **h**, Z = CF_3; **i**, Z = $C{\equiv}C_3H_5$-*c*

Most of the preceding conclusions are based on kinetic acidity determinations and the assumption that relative rates reflect relative carbanion stabilities. This assumption has been appropriately challenged[51]; however, the limited equilibrium acidity data that are available[52] are in complete accord with the above summary (see Table 2).

TABLE 2. Equilibrium acidities in DMSO solution[52]

Z	pK_a Me_2CHZ (**11**)	pK_a *c*-C_3H_5Z (**10**)
NO_2	16.9	ca. 27
SO_2CF_3	21.8	26.6
COPh	26.3	28.2
SO_2Ph	32	32

The diminished acidity of cyclopropyl acids **10** relative to the isopropyl analogs **11** where Z is a resonance stabilizing, i.e. conjugating, substituent may be understood on the basis that such groups as NO_2 and RCO require planarization of a nominally pyramidal carbanionic center in order to realize their full effect. In the cyclopropyl case, an increase in planarity at the α-carbon also means an increase in bond angle strain (I strain) of up to ca. 13 kcal mol^{-1} by analogy to the strain energy increase (13.5 kcal mol^{-1}) for methylenecyclopropane compared to cyclopropane[53]. In addition to ring strain effects, any loss of s character in the carbanionic orbital diminishes the inherent relative stability of the cyclopropyl anion.

The mutually exclusive anion stabilizing effects of conjugation vs. hybridization, as evidenced by the weakened acidity of the cyclopropyl analog, has been used to evaluate the planarizing effects of substituents whose π-conjugative ability is in question[52, 54]. For example, the data in Table 2 strongly suggest that trifluoromethylsulfonyl stabilized carbanions have planar structures[52, 54] similar to nitronate and enolate ions, whereas the analogous benzenesulfonyl ions are, arguably, non-planar[45, 54]. The former conclusions do not apply to the structure of the substituted cyclopropyl anions since planarization is necessarily a more energetic process for these systems.

Direct experimental evidence bearing on the structure of the parent cyclopropyl anion is limited (*vide infra*); however, a variety of *ab initio* and semi-empirical calculations predict a non-planar (pyramidal) structure[55, 56] with an inversion barrier most reasonably estimated to be in the range 17–21 kcal mol^{-1}. The magnitude of this energy barrier to planarization is to be contrasted with the 5–6 kcal mol^{-1} barrier to inversion of unstrained or open chain carbanions[55]. Clearly the latter energy barrier is too low to maintain the configurational integrity of these carbanion systems; however, there are, not surprisingly, a number of enantiomerically stable (chiral) carbanions in the cyclopropyl series, particularly in the 2,2-diphenylcycloprop-1-yl system (**12**)[57–62]. Table 3 provides a listing of those cyclopropyl systems showing a strong to moderate degree of configurational stability at least under the specified conditions of observation. The carbanions (**12a–h**) were prepared

TABLE 3. Configurational stability of some cyclopropyl anions

Cyclopropyl anion	Method[a]	Solvent	T(°C)	% Retention	Ref.
12a	A	Et_2O	28	100	57
	B	Toluene	Reflux	100	58
12b	B	Benzene	Reflux	ca. 100[b]	56, 58
12c	B	Toluene	Reflux	ca. 100[b]	58
12d	B	Xylene	Reflux	ca. 100[b]	58
12e	C	THF	−72	98–100	59
	C	THF	−5	0.3	59
12f	D	MeOH	75	99–100	60
	E	Et_2O	25	0.0	60
12g	D	MeOH	75	27	61
12h	B	Benzene	Reflux	ca. 100[b]	62
13a, 13b	F	THF (d_8)	−60	100[c]	63
	F	THF (d_8)	4	0.0[d]	63
10i	F	Benzene	34	100[c]	64
	F	Benzene/THF	34	0.0[d]	64
	F	THF	R.T	100[c]	65

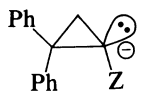
[a] Method A: Br–Li exchange, *n*-BuLi/Et_2O followed by CO_2 quench. Method B: $NaNH_2$ promoted Haller–Bauer cleavage of phenyl ketone. Method C: LDA/THF, −72°C, quench with MeI or MeOD. Method D: H–D exchange vs. racemization using NaOMe. Method E: LDA/Et_2O at 25°C. Method F: DNMR.

[b] Percent retention not given, but essentially unracemized.

[c] Total retention in this case means slow interconversion of enantiomeric or equivalent forms on the NMR time scale

[d] Rapid interconversion of enantiomeric or equivalent forms.

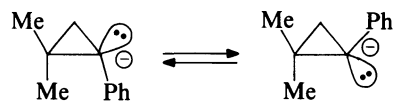
from optically active precursor, quenched (Methods A–E, Table 3), and the configuration of the product determined by optical rotation.



(12)

a, Z = Me; **b**, Z = Cl; **c**, Z = F; **d**, Z = OMe

e, Z = N=C; **f**, Z = C≡N; **g**, Z = PhCO; **h**, Z = $SiMe_3$



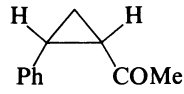
(13a) (13b)

In terms of their electronic characteristics and their effect on carbanion structure the substituents represented in Table 3 arrange themselves into three distinct groups. The first grouping consists of the non-conjugating, inductively stabilizing or destabilizing substituents, the corresponding anions of which, i.e. **12a**–**12d**[56–58], and **12h**[62], exhibit marked configurational stability at room temperature or above. It would appear that these anions

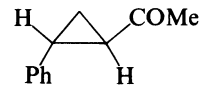
are pyramidal in structure with inversion barriers approaching that calculated for the parent anion (*vide supra*).

The second classification comprises those substituents having a weak conjugative component along with a moderate inductive electron withdrawing effect. Falling into this group are specifically the isocyano, phenyl, and cyclopropylethynyl substituents and their respective anions **12e**[59], **13**[63] and **10i**[64]. The 2,2-dimethyl-1-phenylcyclopropyl anion **13a** (or **13b**) is configurationally static at $-60°C$, but on warming the two methyl singlets broaden and eventually coalesce. The calculated activation free energy at $+4°C$ is 13.4 kcal mol^{-1}. By contrast, at room temperature under similar solvent conditions (Table 3, last entry) cyclopropyllithium displayed the NMR pattern expected for the pyramidal structure[65]. Although studied by a different technique, the isocyano anion **12e** showed very similar behavior to **13a**. The conclusion follows that cyclopropyl anions stabilized by weak resonance acceptors maintain a pyramidal structure although the deviation from planarity may well be diminished.

The final category, encompassing as it does the strongly stabilizing conjugators such as cyano, nitro and carbonyl, provides the most interesting structural puzzle. As previously discussed, the kinetic and equilibrium acidity data for the cyclopropyl ketones provided evidence for planarization at the carbanionic center. Nevertheless, keto anion **12g** affords moderate (27%) retention of configuration upon H–D exchange in methanol while the cyano analog exhibits complete retention of optical activity under similar conditions. In what may be regarded as a related example, *cis*-1-acetyl-2-phenylcyclopropane (**14**) was reported[66] to undergo H–D exchange of its 1-H in MeOD-D_2O/NaOD at three times the rate for isomerization of **14** to the *trans* isomer **15**. While this latter result would appear to represent a further case for configurational integrity for a carbonyl stabilized cyclopropyl anion, the relative merits of the thermodynamic driving force for isomerization vs. protonation from the least hindered face of the cyclopropyl enolate ion are difficult to assess. Likewise, to answer the question of whether such highly stabilized cyclopropyl anions have fully planar limiting structures or whether they retain partial pyramidal character will require more definitive data than presently available. It is tempting, however, to suggest a continuum of structural possibilities between the idealized pyramidal and planar geometries depending on the delocalizing power of the substituent.



(14)



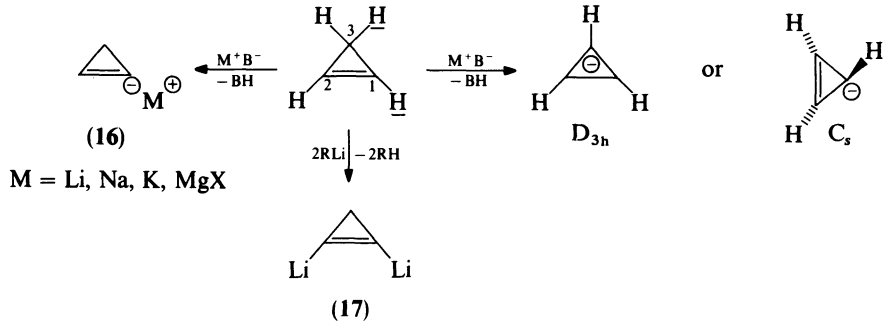
(15)

D. Unsaturated Derivatives of Cyclopropane

1. Cyclopropenes

The superb general review by Closs must still be regarded as the essential primer in cyclopropene chemistry despite its 1966 publication date[67]. The newest review, that by Halton and Banwell in this volume (Chapter 21), clearly illustrates the enormous growth in this field in the past two decades.

In connection with acidity, the introduction of a carbon–carbon double bond into the cyclopropane ring has two obvious effects: (*a*) the overall ring strain (54.5 kcal mol^{-1} [68]) is increased by a factor of two; (*b*) the proton degeneracy is lifted and two sets of potential carbon–acid sites must be considered, i.e. vinyl (C_1–H) and allylic (C_3–H), as shown in Scheme 1. Through its acetylenic character ($^1J_{CH} \cong 220$ Hz; 44% s)[20] the vinyl hydrogen of cyclopropene, or a related derivative, shows enhanced acidity ($pK_a \cong 30$[69]) compared to



(16)

M = Li, Na, K, MgX

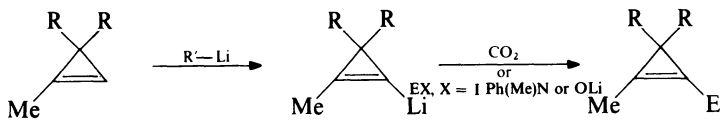
(17)

SCHEME 1

cyclopropane hydrogens or its own allylic hydrogens (Table 1). Analogous to acetylene, cyclopropene reacts with strong, essentially irreversible bases such as alkyllithiums[70], alkali amides[71] or Grignard reagents[72] to afford the 1-metallocyclopropenes **16** (M=Li, Na, K, MgX) in generally good yields. Alkylation of **16** leads to the otherwise difficultly accessible 1-substituted cyclopropenes[73]. If two equivalents of alkali amide and alkylating agent are employed, moderate yields of the 1,2-dialkylcyclopropene can be realized[73]; however, NMR evidence indicates that the 1,2-dimetallocyclopropene is not an intermediate[71]. There is a report of the formation of 1,2-dilithiocyclopropene (**17**) on treatment of cyclopropene with two equivalents of methyllithium[70].

As further illustrated in Scheme 2, the 1-methyl- and 1,3,3-trimethylcyclopropene are rapidly metallated with organolithium reagents in ether to afford stable solutions of the 1-lithiocyclopropenes (**18**)[67, 74, 75]. In comparison, solutions of the metallocyclopropenes (**16**) are significantly less stable and even at −40°C are observed to degrade slowly to a mixture of dimeric and trimeric products apparently formed by nucleophilic addition of **16** to the highly reactive cyclopropene π system[71]. Alkylation of **18** (R=H or Me) with methyl iodide produced 1,2-dimethyl-[76] and 1,2,3,3-tetramethylcyclopropene[67]. The trimethyl derivative **18** (R = Me) has also been carbonated[67, 75] and acylated[67] to afford the corresponding 2,3,3-trimethylcyclopropene carboxylic acid, methyl ketone and carboxaldehyde.

The effect of the cyclopropene double bond on acidity of the allylic (C_3–H) protons is striking in comparison to the situation for the vinyl (C_1–H) protons. As the data in Table 1 reveal, cyclopropene is at least 10 pK units less acidic than cyclopropane. On classical grounds, resonance stabilization of the cyclopropenyl anion (D_{3h} structure, Scheme 1) should provide an acid-strengthening effect; however, increased ring strain associated with planarization of the final ring carbon could offset this stabilization. If π-conjugative effects are considered unimportant, then by analogy to the cyclopropyl anion the nonplanar C_s



(18)

R′ = Ph, Me, or *n*-Bu R = H, Me R = H; E = Me

R = Me; E = Me, CO_2(H), MeCO, CHO

SCHEME 2

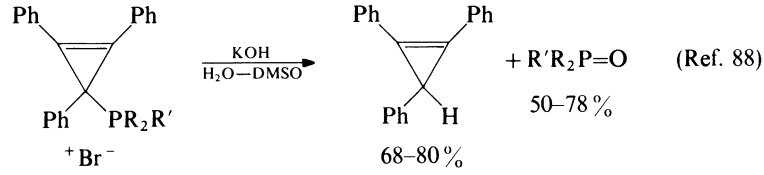
anion (Scheme 1) becomes an attractive structural alternative for $(C_3H_3)^-$. These structural possibilities will be discussed later from a more theoretical standpoint; however, qualitatively, inductive effects associated with the double bond, as well as increased s character in the lone-pair orbital (the ring allylic C–H bonds in 1-methylcyclopropene have 34% s character compared to 32% for cyclopropane methylene C–H bonds[67]) would again be expected to stabilize this anion relative to the cyclopropyl anion. Clearly, classical electronic concepts are incapable of explaining the apparent instability of the cyclopropenyl anion compared to the allyl or cyclopropyl anions.

As the simplest Hückel 4π-electron system the cyclopropenyl anion may be regarded as the prototype for *anti*-aromaticity in that it is less stable than its open-chain analog according to theory[77, 78] and experiment[26, 28]. Furthermore, Hückel theory[77] as well as more sophisticated calculations[78–80] predict that the triplet $D_{3h}(^3A_2')$ anion should be more stable than the singlet $D_{3h}(^1E')$ structure. Interestingly, however, recent *ab initio* MO calculations affirm that both singlet and triplet cyclopropenyl anions severely deviate from planarity with the singlet $C_s(^1A')$ having the predicted lowest energy (ground state) structure[80]. These authors state that 'these "antiaromatic" species which have assumed planarity are not realistic'[80].

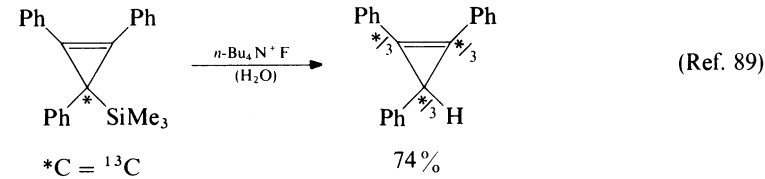
The calculated singlet $C_s(^1A')$ ground state structure is of particular interest as it reveals a strong antibonding interaction between the lone-pair orbital and the π orbitals of the double bond[80]. This interaction is reflected in lengthening of the C–C single bonds (1.591 vs. 1.516 Å in cyclopropene) as well as in bending of the anionic carbon's C–H bond out of the ring plane by almost 70°. In addition the olefinic C–H bonds are tipped out of the ring plane in the opposite direction to the extent of about 9° which further relieves repulsive π interactions. Finally, the calculated inversion barrier of 35.4 kcal mol^{-1} for the C_s anion is considerably higher than that calculated for the cyclopropyl anion (*vide supra*). All of the above structural features for the calculated ground state of $(C_3H_3)^-$ point to π-electronic destabilization or *anti*-aromaticity as delineated by Breslow[77, 81].

There are two additional features of the hydrocarbon, cyclopropene, which have not been considered and which may contribute to its reduced kinetic and thermodynamic acidity. First of all, the reversed sign (polarity) of the dipole moment of cyclopropene compared to other alkenes, including cyclobutene, and its larger than usual magnitude (0.455 D)[82], is indicative of significant electron shift from the double bond to the methylene group[83]. This has been shown to be a result of electron transfer from the π_{cc}-orbital to the $\sigma^*_{CH_2}$ component orbital[83]. Related to this polarity reversal is the observation of enhanced (anisotropic) magnetic susceptibility for cyclopropene which suggests the presence of a sustained diamagnetic ring current[84]. Greenberg and Liebman note that, taken together, 'the dipole moment and diamagnetic ring current indicate appreciable "cyclopropenium hydride" character for cyclopropene'[85]. Charge separation in the ground state of cyclopropene thus opposes charge development in the transition state for proton removal. Extrapolation to complete proton removal leads to the prediction that the highest lying electron pair in the anion would only be loosely bound, a conclusion supported by recent calculations[80].

Substituent effects on the acidity of cyclopropenes are in the expected direction as revealed in Table 1. Alkyl groups are strongly destabilizing while phenyl groups provide moderate stabilization whether located on the double bond or at the methylene carbon[26]. For example, 1,2,3-triphenylcyclopropene, with a pK_a value of 50, should be at the threshold of observable deprotonation using strong bases; however, all attempts at generation and detection of 1,2,3-triphenylcyclopropenyl anion in solution have, as yet, failed, primarily due to the proclivity of the cyclopropene double bond towards nucleophilic addition of the base[67, 86]. Even the sterically hindered base, triphenylmethide, has been observed to add to the double bond of 1,2-diphenylcyclopropenyl ester (**19**)[87]. Importantly, there was no evidence for the formation of the cyclopropenyl anion

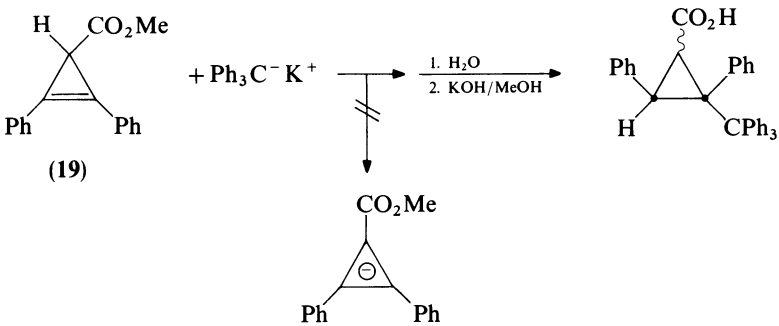


R = Ph; R' = Me
R = Me; R' = Ph
R = R' = *n*-Bu



SCHEME 3

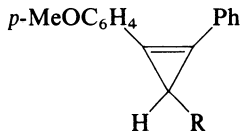
(**20**). The alternative approaches[88, 89] summarized in Scheme 3 implicate the formation of the 1,2,3-triphenylcyclopropenyl anion; however, other mechanistic interpretations not involving the free carbanion are clearly possible.



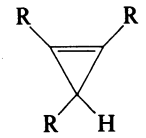
The MNDO optimized geometry for the triphenylcyclopropenyl anion has a planar three-membered ring with the phenyls twisted by only 12° relative to the ring plane[80]. The overall symmetry is C_{2v} with the C(1)–C(2) bond distance (1.517 Å) considerably longer than that (1.392 Å) for the other two C–C bonds. Furthermore, this allyl-type structure is calculated to have only 45% of the negative charge remaining in the cyclopropenyl ring[80].

The calculated planarity of the triphenylcyclopropenyl anion is surprising, on first inspection, in view of the pyramidal structure of the 1-phenylcyclopropyl anion (*vide supra*); however, completely analogous experimental results have been obtained by Breslow and coworkers for diarylcyclopropenes carrying a strong anion stabilizing group at the methylene carbon[77, 81, 90]. Thus, hydrogen/deuterium exchange of optically active 3-cyano- and 3-benzoyl-substituted cyclopropenes **21a** and **21b** under basic conditions proceeds with little or no retention of configuration, suggesting that the degree of

planarization at C(3) is considerably greater than in analogous cyclopropyl compounds even though anion formation in the cyclopropene derivative is considerably more difficult. Breslow and Douek[90] rationalized the cyclopropene results on the basis of *anti*-aromaticity arguing that electronic repulsion at the anionic ring carbon demands extensive charge delocalization into the pendant conjugating group(s) whether it (they) be aryl, cyano, or benzoyl, thus flattening the ring.



21a; R = CN: $k_e/k_r = 4$
21b; R = COPh: $k_e/k_r = 1$



22a; R = CN
22b; R = COPh

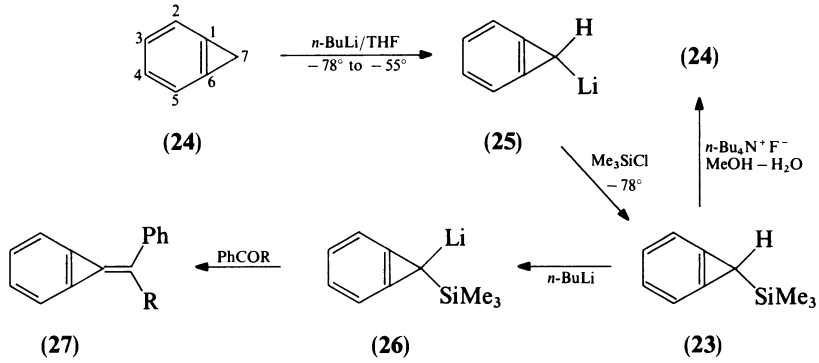
Efforts directed towards the synthesis of stable, perhaps isolable, cyclopropenyl anions having three identical anion stabilizing groups, such as cyano or benzoyl, have been attempted without much success. Tricyanocyclopropene (**22a**) could not be prepared except as a transient intermediate which could be trapped with diphenylisobenzofuran[91]. The corresponding triketone (**22b**) was obtainable, but attempted generation of the corresponding anion was thwarted by conjugate (Michael) addition of the base to the double bond[92]. The cyclopropenyl anion remains an illusive species!

2. *Benzocyclopropene*

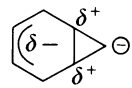
Benzocyclopropenes (cyclopropabenzenes) have been reviewed by Halton[93] and in this volume by Billups and Moorehead.

The fusion of cyclopropene to a benzene ring has a remarkable effect on the acidity of the allylic/benzylic methylene protons. Thus, 7-benzocyclopropenyltrimethylsilane (**23**) was found to undergo base-catalyzed (NaOH) desilylation in aqueous methanol solution nearly 64 times as rapidly as benzyltrimethylsilane, indicating that benzocyclopropene (**24**) is more acidic than toluene[94]. On the basis of the reported[95] linear correlation of pK_a values for a series of aralkyl hydrocarbons (RH) with the log k_{rel} for base-catalyzed cleavage of the corresponding silanes (Me_3SiR), the pK_a for **24** was estimated to be about 36. This compares favorably with the estimated value of 41 (Streitwieser scale, Table 1) for toluene. Consistent with this level of acidity, metallation (*n*-BuLi) of **24** at low temperature (Scheme 4) afforded 7-lithiobenzocyclopropene (**25**), the first stable anion derivative in this series[94]. No spectroscopic data have been reported for **25**, but its presence in solution is demonstrated by the isolation of silane (**23**) on quenching (−78°C) with chlorotrimethylsilane. Silane (**23**) has been recently employed in the synthesis of the substituted methylenecyclopropabenzenes (benzotriafulvenes) (**27**) via Peterson olefination of the respective phenyl ketones[95]. Deprotonation of **23** with *n*-butyllithium apparently generated the lithiated silane **26** which is also a benzocyclopropenyl anion derivative.

Comparison of the ^{13}C–H coupling constants for benzocyclopropene (**24**) (178 ± 2 Hz[96]) and 1-methylcyclopropene (172 Hz[67]) provides little insight into the enhanced acidity of **24**. On the other hand, STO-3G calculations of the energy difference between parent hydrocarbons and their respective anions led to *predicted* pK_a values of 33, 41 and 60 for **24**, toluene, and cyclopropene, respectively[97]. The source of the remarkable stability for the benzocyclopropenyl anion appeared to be associated with polarization of the π-electron system as represented in structure **28** together with concomitant σ-induction of negative charge to C(1) and C(6) from the carbanion center (C(7)). Therefore, charge



SCHEME 4



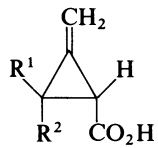
(28)

stabilization (delocalization) in the benzocyclopropenyl anion is a combination of σ-and π-effects, the latter of which (i.e. **28**) cannot be operative in the cyclopropenyl anion. In apparent agreement with this analysis, the calculated geometry at the carbanion center is pyramidal with only a slight amount of flattening compared to the cyclopropenyl anion[97].

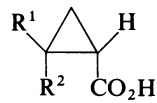
3. *Methylenecyclopropanes*

Analogous to previously developed arguments, the effect of the exocyclic double bond of methylenecyclopropane on acidity of the C(2) (or C(3)) ring protons should be acid-strengthening, although modulated somewhat by the increase in ring strain associated with planarization at the developing carbanion center. In line with this assessment, the methylenecyclopropane carboxylic acids **29–31** show greatly (10^4–10^5) enhanced rates of base-catalyzed hydrogen–deuterium exchange of the ring proton compared to the analogous cyclopropane derivatives **32–34**[98]. Similar observations were made for the unsaturated nitrile **35**[81]. The carbanion derived from **29**, **30**, or **31** should be planar or nearly planar; however, the parent methylenecyclopropyl anion should be decidedly non-planar, similar to the 1-phenylcyclopropyl carbanion (*vide supra*). Experimental evidence bearing on this question does not appear to be available.

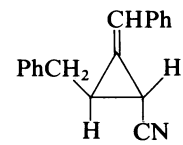
In contrast to the facile generation and trapping of the allylic anion from diphenylmethylenecyclobutane (**36**; Scheme 5) treatment of diphenylmethylenecyclopropane (**37**) with



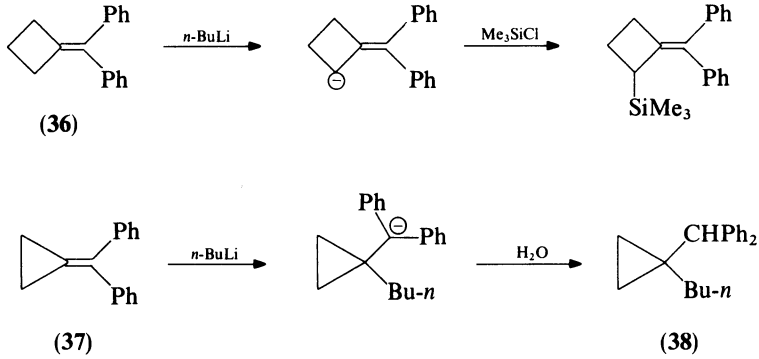
29; $R^1 = R^2 = H$
30; $R^1 = H$; $R^2 = CO_2H$
31; $R^1 = CO_2H$; $R^2 = H$



32; $R^1 = R^2 = H$
33; $R^1 = H$; $R^2 = CO_2H$
34; $R^1 = CO_2H$; $R^2 = H$



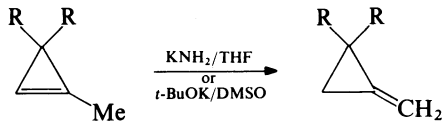
(35)



SCHEME 5

n-butyllithium produced extensive polymerization along with ca. 30% of the hydrocarbon **38** after quenching with water[99]. The additional strain energy that would develop in the allylic anion derived from **37**, coupled with the increased reactivity of the highly strained π-bond of **37** apparently promotes nucleophilic addition to the double bond rather than proton abstraction by the alkyllithium. This result is reminiscent of the problems encountered with the diarylcyclopropenes in that addition reactivity of the double bond precludes generation of the desired carbanion by strong nucleophilic bases.

The rapid and quantitative isomerization of 1-methylcyclopropene[100], and related methyl substituted cyclopropenes[67,101], to the corresponding methylenecyclopropanes is indicative of relief of ring strain in the transition state which is predominantly carbanionic



R = H or Me

in character. For this conclusion to be valid means that the anion derived from 1-methylcyclopropene (or methylenecyclopropane) must be methylenecyclopropanide in nature and, furthermore, must be non-planar. Simultaneous observation of the isomerization of 1-alkylcyclopropenes with rates and sites of deuterium incorporation would shed vastly more light on this interesting rearrangement.

IV. BASICITY

A. Theoretical Aspects

The facility of cyclopropanes to react with proton acids and form protonated cyclopropanes—the stability of the complex formed relative to the stability of the cyclopropane—is the basicity of cyclopropane. Protonated cyclopropanes are well established as discrete structural entities and in special circumstances can be generated under conditions where they have a sufficient lifetime to allow spectral investigation. The complex of proton plus cyclopropane can revert to starting species, i.e. cyclopropane and proton, or undergo further reaction, whether rearrangement or addition of a nucleophile.

The reversion reaction can be probed by isotope labelling experiments and kinetic studies, and rearrangement and nucleophilic attack by labelling studies or, for sufficiently dissymmetric cyclopropanes, by a study of product structure often combined with labelling studies.

Solution phase reaction of an electrophile with cyclopropane(s) requires favorable interaction of the LUMO of the electrophile with the HOMO degenerate, symmetric or *anti*-symmetric, orbitals of cyclopropane[102]. The 1s orbital of H^+ or one lobe of the p-orbital of a carbocation or electrophile can react with the *anti*-symmetric (3e′) orbital (Figure 2) with consequent reduction in bonding in adjacent carbon–carbon bonds and relief of C(2)–C(3) antibonding. Completion of this carbon–proton or carbon–electrophile bond results in a 'corner-protonated cyclopropane' (**39**). Reaction of an electrophile, e.g. proton or carbocation, with the degenerate symmetric 3e′ orbital (Figure 3) will give an

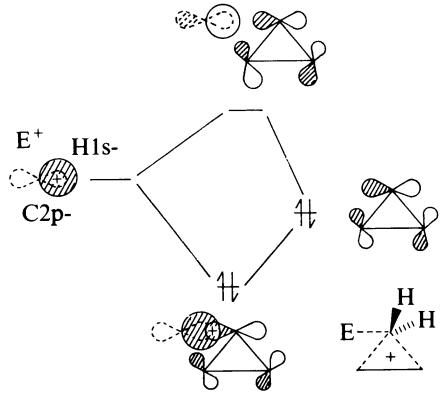


FIGURE 2. Interaction of H^+ 1s orbital or C^+ p orbital with the cyclopropane *anti*-symmetric 3e′ orbital.

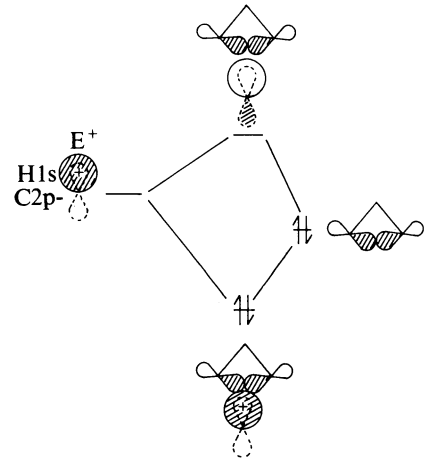
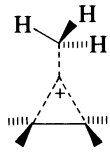
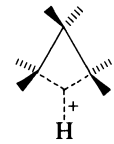


FIGURE 3. Interaction of H^+ 1s orbital or C^+ p orbital with the cyclopropane symmetric 3e′ orbital.

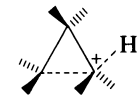
edge-protonated species (**40**). The reader should note that structures **39** and **40** are meant to represent carbocationic species having a three-center two electron bond in the fashion proposed by Olah[102a]. Thus, structure **39a** (or **39b**) depicts an ethylenemethonium ion involving overlap of a methyl cation orbital with the π-system of an ethylene unit.



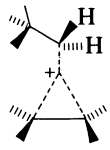
corner-protonated cyclopropane (**39a**)



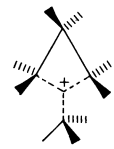
edge-protonated cyclopropane (**40a**)



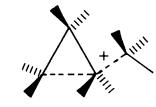
corner attack by proton (**41a**)



corner-alkylated species (**39b**)



edge-alkylated species (**40b**)



corner attack by electrophile (**41b**)

Similarly, **40a** (or **40b**) represents a proton 1s orbital overlapping with the edge orbitals of a cyclopropane ring to again produce a three-center two electron bond. All carbons in ions **39** and **40** are formally tetracoordinate. There is in fact good evidence for the existence of edge-protonated cyclopropane[103] in the gas phase. The microwave spectroscopy of a dimeric species formed on reaction of HCl with cyclopropane has been interpreted as the edge-on form of the dimer of C_{2v} symmetry in which the HCl molecule lies in the plane of the ring along the C_2 axis and forms a hydrogen bond to the future midpoint of one of the C–C bonds. An alternative mode of reaction possible for a 'small' or 'hard' electrophile such as a proton will involve electrophile interaction with the symmetrical 3e′ orbital at the corner of the cyclopropane ring (Figure 4) resulting in weakening of mainly one adjacent carbon–carbon bond as illustrated by structures **41**. Involvement of the electrophile with both the degenerate 3e′ orbitals (corner attack) will result in weakening of both adjacent C–C bonds and consequent bond lengthening but with the bond *anti* to the attacking electrophile lengthening to a greater extent. π-Type interaction of electrophile and cyclopropane is possible and may become important in reaction of the *anti*-symmetric 3e′ orbital of cyclopropane with a metal atom (Figure 5).

For sufficiently dissymmetric cyclopropanes, these various modes of reaction have consequent stereochemical implications. Implicit in edge attack (Figure 3) is retention of configuration in the development of the new carbon–electrophile bond, while attack by electrophile as shown in Figure 4 would result in inversion of configuration at that center. The stereochemistry resulting from attack of the electrophile on the *anti*-symmetric 3e′

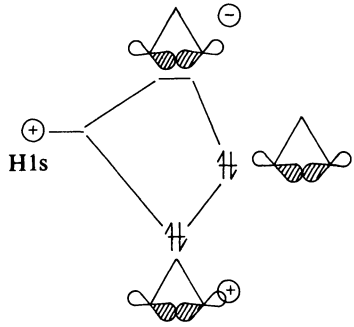


FIGURE 4. Interaction of H^+ 1s orbital with the symmetric 3e′ orbital of cyclopropane

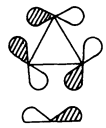
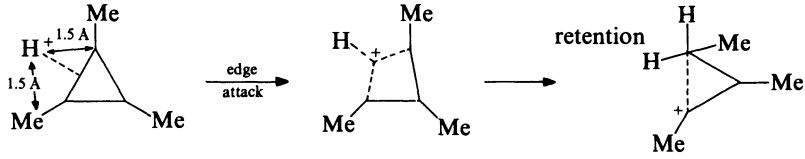


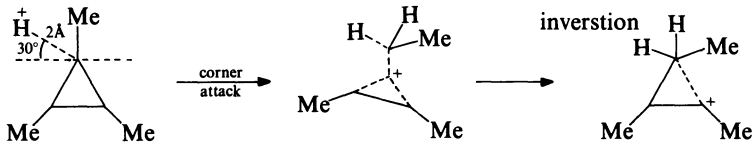
FIGURE 5. π-Type interaction with the *anti*-symmetric 3e′ orbital of cyclopropane.

orbital (Figure 2) is more complex and depends upon which of the adjacent bonds ruptures since both are weakened by orbital mixing with electrophile.

Wiberg and Kass[15], in a particularly appropriate study, have considered the approach of a proton to 1,2,3-trimethylcyclopropane in two different relative orientations and using a gradient method allowed the structures to relax, thereby simulating two possible reaction coordinates for reaction of a proton with the cyclopropane. The first configuration (Scheme 6) involves a proton at the edge of the cyclopropane 1.5 Å from the proximate carbons–'edge attack'. In the second configuration (Scheme 7), the proton was placed 2 Å away from one of the ring carbons along a line 30° above the horizontal line through the carbon as shown—'corner attack'. For the former configuration of attack, namely 'edge



SCHEME 6



SCHEME 7

attack', as the structure relaxed the proton moved closer to the carbons and the carbon–carbon bond distance increased until the structure resembled that of a slightly distorted edge-protonated cyclopropane. As the proton began to move toward one of the carbons, the C–C distance continued to increase. From this theoretical study, edge attack therefore occurs with retention of configuration. In the alternative configuration of attack, namely 'corner attack', as the proton approached both adjacent C–C bonds increased in length, but the one on the side away from the proton increased more rapidly, leading to the same final structure as for edge attack except that the process occurred with inversion of configuration. These calculations compute the two modes of reaction to be comparable in energy. Neither reaction coordinates requires a corner-protonated cyclopropane structure on the reaction pathway.

B. Protonated Cyclopropane

To attempt to define in some detail the reaction of a proton with cyclopropane, calculations of the relative energy of several different configurations of protonated cyclopropane[104-111] have been carried out (Table 4). These calculations have resulted in conflicting conclusions; however, all levels of the various theories[104-109] result in the face-protonated cyclopropane (**48**) with the proton involved with the S(2a') orbital being prohibitively unfavorable. Furthermore, the 2-propyl cation (**49**) is calculated as the lowest energy configuration and thus is in agreement with experimental determination of the heat of formation of the 2-propyl cation being 16 kcal mol^{-1} below that of the 1-propyl cation[112,113]. Evidence from mass spectral measurements also shows the 1-propyl cation to be unstable and to rearrange to the 2-propyl cation[113,114].

Early calculations at the STO-3G level by Pople and coworkers[104] indicated the 1-propyl cation (**42**) to be lower in energy than edge (**47**) and corner-protonated cyclopropanes **45** and **46**. Higher level 4-31G calculations[104] reduced both the energy of corner-protonated cyclopropane (**46**) and 1-propyl cation in conformations **42** and **43**. Calculations at the STO-3G, 4-31G and at the 6-31G* levels[105] favor a conformation of the 1-propyl cation (**42**) where the C(2)–C(3) σ-bond can hyperconjugate effectively[104,115] with the vacant p orbital at C(1). This cation at the HF/6-31G* level was suggested to convert without activation to corner-protonated cyclopropane (**45**, **46**) on optimization.

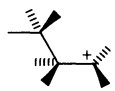
The question of whether the methyl group in the corner-protonated species is freely rotating is important. The relative energies[104,105] of the two conformations of corner-protonated cyclopropane, **45** and **46**, would indicate no substantive barrier to methyl rotation in the delocalized corner-protonated configuration. Calculations[104,109] on distorted 1-propyl cation (**44**) where the C(2) methyl bond is in the plane of the vacant p orbital and moved towards this center suggest the 1-propyl cation falls downhill to corner-protonated cyclopropane and the 2-propyl cation. The potential surface between the 1-propyl cation and protonated cyclopropane has not been established. Inclusion of d-functions at the 6-31G* level[105,117] lowered the calculated energies of the edge (**47**), corner (**45**) and 1-propyl (**42**) configurations with the corner configuration (**45**) being the lowest in energy and edge-protonated cyclopropane (**47**) higher in energy than the 1-propyl cation (**42**).

MINDO/2' calculations[107,108] which give heats of formation, favored edge protonation, **47**, to corner protonation, **45**, by as much as 7.2 kcal mol^{-1}. Both configurations were calculated as lower in energy than the 1-propyl cation (**42**). Higher level MINDO/3 calculations[109] raised the energy of the edge-protonated configuration (**47**) and the energy of the corner-protonated configuration (**45**), the net result being the favoring of edge over corner protonation by 5 kcal mol^{-1}, but both configurations were more stable than the 1-propyl cation (**42**). CEPA calculations[106] supported the 1-propyl cation (**42**)

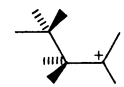
TABLE 4. Relative energies (heats of formation) of $C_3H_7^+$ isomers (kcal mol^{-1}) compared with 2-propyl cation

	MP4(SDQ)[a;116]	MP3[a;15;116]	MP2[a;116]	HF/6-31G**[a;116]	6-31G*[c;105]	4-31G[104]	STO-3G[104]	CEPA[106]	MINDO/2'[d;107,108]	MINDO/3[d;109]
Face **48**					130.1	139.6	161.0	99.71	56.0	88.3
Edge **47**	(8.7)[b]	(7.8)[b] 8.1[e]	5.0	17.4	19.1	27.1	27.1	2.49	−3.9	7.5
Corner **46**					13.1	17.4	22.9			
Corner **45**	(8.2)[b]	(7.2)[b] 5.8[e]	4.7	13.7	13.0	17.3	22.8	7.52	3.5	12.3
1-Propyl **43**					18.8	19.4	21.0	18.55		
1-Propyl **42**	(19.7)[b]	(19.8)[b]	19.9	18.8	17.0	17.4	19.7	16.54	24.5	18.6
Distorted 1-propyl **44**					14.1	16.9	20.5			
2-Propyl **49**	0	0 3.9	0	0	0	0	0	0	0	0

[a] 6-31G** basis and HF/6-31G* optimized geometries.
[b] Projected estimates based on the third and fourth order effects on the 6-31G* basis.
[c] Includes d-functions on carbon[117].
[d] Heats of formation.
[e] Calculated values for cyclopropane + $MeOH_2^+$ → edge- or corner-protonated cyclopropane; cf. propene + $MeOH_2^+$, 3.9 kcal mol^{-1}.

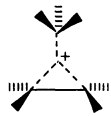


1-propyl
(42)

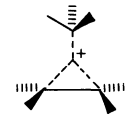


1-propyl
(43)

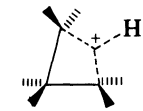
distorted 1-propyl
(44)



corner
(45)

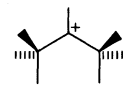


corner
(46)



edge
(47)

face
(48)



2-propyl
(49)

being higher in energy to edge- and corner-protonated cyclopropane. In these calculations, edge-protonated cyclopropane (**47**) was favored to corner (**45**) by ca. 5 kcal mol^{-1}.

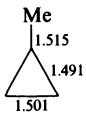
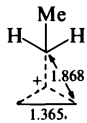
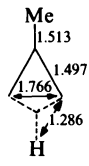
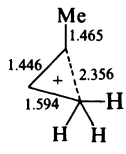
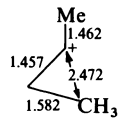
A protonated cyclopropane species with a lifetime exceeding 10^{-7} s in the gas phase and about 8 kcal mol^{-1} less stable than the 2-propyl cation (**49**) has been observed[118-120] experimentally by Cacace and coworkers[120] and earlier by Chong and Franklin[114] and McLafferty and coworkers[113]. From MINDO/3 calculations[109], this species could be the edge-protonated species (**47**). Similarly from CEPA calculations[106] it would be the edge-protonated species **47**, but *ab initio* calculations at the highest level effected at that time, namely the 6-31G* level[105], indicated no species with an appropriate energy although the corner-protonated species (**45**) was suggested as appropriate. Subsequent higher level calculations[116] HF/6-31G** and MP2 with 6-31G** basis and HF/6-31G* optimized geometries where the p-function on hydrogen is accounted, reduced the energy levels of the edge- and corner-protonated cyclopropane to comparable values; MP2; 5.0, 4.7 kcal mol^{-1} respectively above 1-propyl cation (**42**). Projected estimates based on the third and fourth order effects on the 6-31G* basis (MP3, MP4(SDQ)) increased the energy values to comparable with experiment; MP4 (SDQ) edge (**47**), 8.7 kcal mol^{-1}; corner (**45**), 8.2 kcal mol^{-1} above 1-propyl cation (**42**). Force constants for the edge-protonated configuration **47** with a 3-21G basis suggested it was not a local minimum, the negative frequency corresponding to conversion to the corner-protonated form **45**. With the larger 6-31G basis set, Pople and coworkers [116] were not able to conclude which form, edge or corner, is the more stable. Wiberg and Kass[15] have calculated energies for the reaction of cyclopropane and $MeOH_2^+$ to obtain 6-31G* MP3 values of edge- and corner-protonated cyclopropane of 8.1 and 5.8 kcal mol^{-1} respectively. Corrections for zero point energies and a change in ΔH in going from 0 to 298 K are small (1 kcal mol^{-1}). Taking all these calculations into consideration, it seems however, likely that the energy difference of edge- and corner-protonated cyclopropane in the gas phase is small.

The energy for the 1-propyl cation (**42**) at the projected MP4 SDQ/6-31G* level is 19.7 kcal mol^{-1} less stable than the 2-propyl cation (**49**) which is higher than the earlier reported experimental value[112], but an even higher experimental value of 23.5 kcal mol^{-1} has been obtained from the photoelectron spectra of the 1-propyl radical[103].

C. Protonated Methylcyclopropane

Wiberg and Kass[15] have calculated (Table 5) the relative energy of protonated methylcyclopropane by geometry optimization for protonation at either the methylene or methine carbons, **52** and **50**, and for an edge-protonated species (**51**) by using both the 3-21G and 6-31G* basis set and applied a second order correction for electron correlation (MP2). An estimate of the third order (MP3) correction was made. The methine-protonated species (**50**) is thus calculated to be 8 kcal mol^{-1} higher energy than the methylene-protonated ion (uncorrected value) (**52**) and this is consistent with the observed preference for Markovnikov-type cleavage. Unlike corner-protonated cyclopropane (**45** and **46**) the calculated lowest energy structure of the methylene-protonated ion (**52**) is markedly unsymmetrical.

TABLE 5. Structures (bond lengths (Å) from 6-31G* calculations) and energies of protonated methylcyclopropanes (kcal mol^{-1}) compared with 2-butyl cation[15]

					
	(50)	**(51)**	**(52)**	**(53)**	
	methine protonated	edge protonated	methylene protonated	lowest energy 2-butyl cation conformation	
3-21G	14.6	25.5	0.5	0	
6-31G*	14.8	17.0	0.5	0	
MP2	6.1	4.7		0	
MP3[a]	(8.6)	(7.5)		0	

[a] Estimated.

The energy of the ion formed from reaction of methylcyclopropane with $MeOH_2^+$ has been compared with the energy of the 2-butyl cation (**53**) formed from similar reaction with *trans*-but-2-ene. The energies of the two hydrocarbons differ by 9 kcal mol^{-1} and since the ΔG^0 for the reaction of methylcyclopropane and *trans*-but-2-ene were essentially the same, the ion from methylcyclopropane must be 9 kcal mol^{-1} higher in energy than the 2-butyl cation. From the calculated values (Table 5), this is inconsistent with the protonated cyclopropyl cation being **52** and indicates that the cation which would be a kinetically controlled product formed in 10^{-7}–10^{-8} s must be the corner- or edge-protonated species **51** or **50**. It should therefore be possible to observe isotope exchange at the methine carbon since protonation should, from the calculations, occur first at this carbon but the reaction would be expected to proceed via cation **52**. For exchange to occur

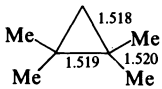
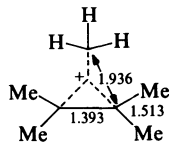
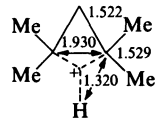
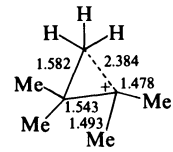
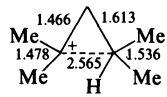
at the methine carbon, the symmetry of cation **50** must be such that the protons at the pentacovalent carbon are, or rapidly become, undistinguishable thereby making for equal possibility of loss of either potentially prochiral hydrogen. These calculations warrant a study of methylcyclopropane with deuterated acid.

The comparability in energy of the methylene-protonated cyclopropane (**52**) and the optimized geometry for the 2-butyl cation (**53**) indicates the potential surface is almost flat in this region.

D. Protonated 1,1,2,2-Tetramethylcyclopropane

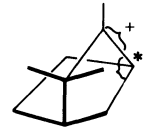
The energies and bond lengths of four protonated 1,1,2,2-tetramethylcyclopropane structures **54**, **55**, **56** and **57** have been calculated by geometry optimization using the 3-21G basis set (Table 6). The unsymmetrical corner-protonated structures **56** and **57** are lower in energy than the edge-protonated **55** or symmetrical corner-protonated structure **54**. While the energy difference between structures **54** and **55**, and **56** and **57**, is expected to be reduced by the inclusion of polarization functions and electron correlation into the calculations the energy differences are such as to predict acid cleavage to involve the latter ions.

TABLE 6. Structures, bond lengths (Å) and energies (kcal mol^{-1}) from 3-21G calculations and optimization of protonated 1,1,2,2-tetramethylcyclopropanes[15]

					
	(**54**)	(**55**)	(**56**)	(**57**)
	corner-protonated	edge-protonated	unsymmetrical corner-protonated	unsymmetrical corner-protonated
3-21G	10.3	21.7	0.0	2.2

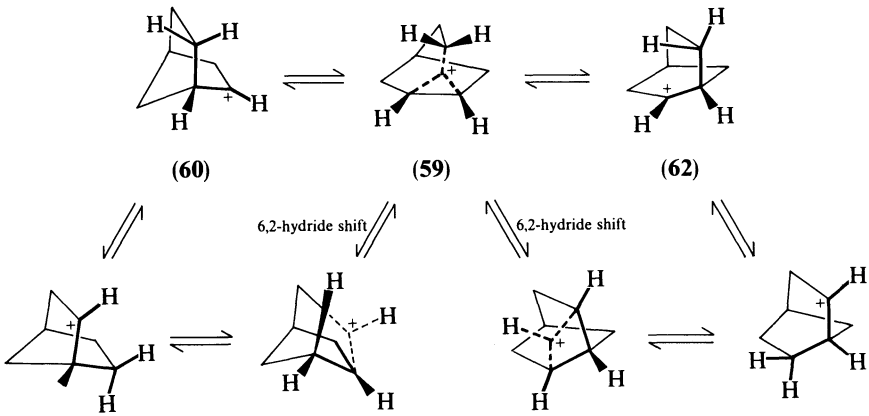
E. Protonated Nortricyclene

The corner-protonated cyclopropane configuration **45** is analogous to the non-classical norbornyl ion at the center of controversy for the past three decades. The non-classical cation concept had its origin with Wilson and coworkers[121] in 1939 who depicted structure **58** as a possible intermediate in the camphene hydrochloride–isobornyl chloride



(**58**)

rearrangement[122]. The extension of this structure to the norbornyl cation by Winstein and Trifan[123–125] was the focal point of the controversy[126–133] and has dictated the need to establish the relative energy of the non-classical symmetrical corner-protonated cyclopropane **59** and the classical norbornyl cation **60** (Scheme 8). Attempts to draw conclusions as to the energy of these cations by inductive reasoning from solvolysis studies and from spectral investigations have led to increasingly detailed and imaginative experiments being undertaken, an intensity of effort on a single problem unmatched in the history of organic chemistry. The corner-protonated non-classical norbornyl ion does not have the same freedom as corner-protonated cyclopropane (**45**) since bridging of the pentacovalent carbon to the carbocyclic system makes rotation of this carbon no longer possible. Complicating any general conclusions drawn from solvolytic or spectroscopic studies is the need to consider the role and effect of solvent and reaction media on the ion and therefore caution must be exercised in extrapolating observations from low temperature spectroscopic studies in super-acid media to intermediates and transition states in solvolytic reactions. In the same way caution must be exercised in interpreting gas phase studies on $C_3H_7^+$ cations with experimental studies in the liquid phase. There is some evidence that the relative energies of simple isomeric secondary and tertiary carbonium ions are similar in the gas phase and in solution[134–137] although the energy of cations may vary significantly when there is different charge delocalization for the ions under comparison and when the counter ions or solvent molecules are good electron donors.[138] Mass spectrometric studies show that the 2-norbornyl cation has exceptional stability in the gas phase[139–142].



(60) (59) (62)

(61)

SCHEME 8

The problems associated with theoretical calculations of the energies of protonated cyclopropane are readily apparent and the norbornyl skeleton increases the complexity of computation. Early quantum mechanical calculations of the MINDO/3[143–145], STO-3G (MINDO/3 geometry)[144] and *ab initio* STO-3G type [144] show the corner-protonated norbornyl cation less stable (~ 1.9[143, 144] (8–13)[145]; 5.9[144] and 4.9[144] kcal mol^{-1} respectively) than the classical structure. STO-3G calculations[144] shows the edge-protonated configuration **61** to be 14.4 kcal mol^{-1} less stable than the classical ion;

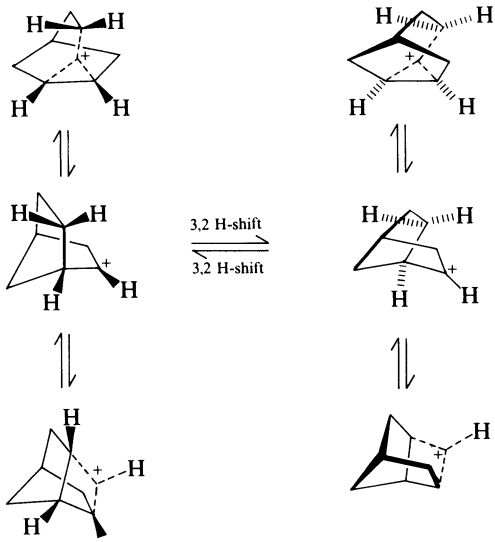
however, Kohler and Lischka[145] suggested that the edge-protonated configuration should be nearly as stable as the corner-protonated structure. These calculations have been regarded as not definitive[146] since electron correlation corrections which favor bridged structures were not explicitly included.

More recent calculations[147] of relative SCF energies of the norbornyl cation with the use of a split valence 4-21G basis set and a gradual procedure augmented by d-polarization functions on all carbons indicated the non-classical form **59** to be 0.2 kcal mol^{-1} more stable than the classical form (**60**). In these calculations, however, the classical geometry can best be described as an unsymmetrically bridged species. Refinement in these calculations[146] using previous 4-21P (and in some cases STO-3G) optimized geometries, electron correlation corrections at the second-order Moller-Plesset MP2 perturbation level and using 4-21P, 6-31G and 4-21D basis augmented by a set of five d-type polarization functions on each carbon resulted in a calculated energy difference between classical norbornyl and corner-protonated norbornyl of 15 kcal mol^{-1} in favor of the bridged structure. Liu[148], on the other hand, calculates stabilization energies of 2.1 and 5.4 kcal mol^{-1} for corner (**59**) and edge- (**61**) protonated norbornyl cations. The edge-protonated nortricyclene (**61**) was calculated by Schaefer and coworkers[147] to be higher in energy (12.4 kcal mol^{-1}) than the non-classical corner-protonated structure **59**. These values must be compared with the value calculated for edge-protonated cyclopropane (8 kcal mol^{-1}) and with the measured activation barrier of 5.9 kcal mol^{-1} [132,149,150] for a 6,2-hydride shift in super-acid media (Scheme 8). This edge-protonated configuration may approximate a transition state structure or an intermediate in the hydrogen transfer.

Two interpretations of the ^{13}C NMR spectrum[151] of the norbornyl cation system generated in super-acid media and measured at 5 K are possible. The spectrum may be attributed to rapid equilibrium between structures with localized charges [**60** $\rightleftharpoons$ **62**] but for this to be the case, very restrictive limits are placed on the barrier to this interconversion such that the exchange frequency is 10^5 s^{-1} or greater. In the absence of a tunneling mechanism[152] classical rate theory requires the activation barrier to be no larger than 0.2 kcal mol^{-1}. On the other hand, the spectrum can be interpreted as that of the non-classical structure. The ESCA spectrum[153–155], the ^{13}C- and ^{1}H-chemical shifts[156,157] and the perturbation isotope effects[158,159] have been interpreted as support for the norbornyl cation being corner protonated in stable ion media. At higher temperatures (ca. 150 K) the 6,2-hydride shift is observed with a barrier of 6.1 kcal mol^{-1} [151,160] (5.9 ± 0.2 kcal mol^{-1})[149]. At higher temperatures again C(3) hydrogen migration to C(2) occurs with an energy barrier of 10.8 ± 0.6 kcal mol^{-1} [149], and this process transfers the charge to the reverse side of the norbornyl system (Scheme 9). The result of these processes occurring concurrently greatly simplifies the ^{13}C- and ^{1}H-NMR spectrum.

The intense interest in norbornyl cation studies and in particular in the corner-protonated non-classical configuration[161–172] have overshadowed studies on protonated cyclopropane itself. In the early years of the non-classical ion debate, attention was focused on the stereochemistry of nucleophilic attack on the norbornyl cation and rationalization of the relative rate difference for solvolysis of the C(2) tosylates of *exo* and *endo*-norbornan-2-ol. This feature of norbornane chemistry remains controversial to this day. Spectroscopic studies of the norbornyl cation have been of fundamental value in establishing information about structure and bonding. The nature, energetics, and the variety of molecular processes which occur, could not have been envisaged without detailed probing. Calculations are proving of increasing value as the sophistication and methods of analyses begin to be more predictive of experimental observations.

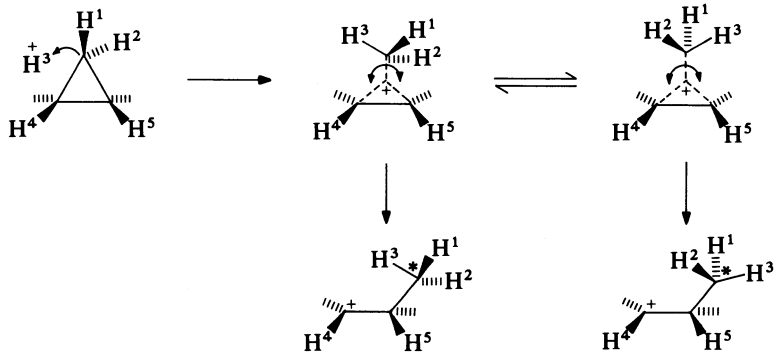
The solvolysis of propyl and bornyl systems and protonolysis of cyclopropane and nortricyclene are two routes to protonated cyclopropanes (Scheme 10). For sufficiently dissymmetric cyclopropanes, corner and edge attack by electrophiles at cyclopropane can be differentiated. This stereochemical division of electrophilic attack is not to be confused



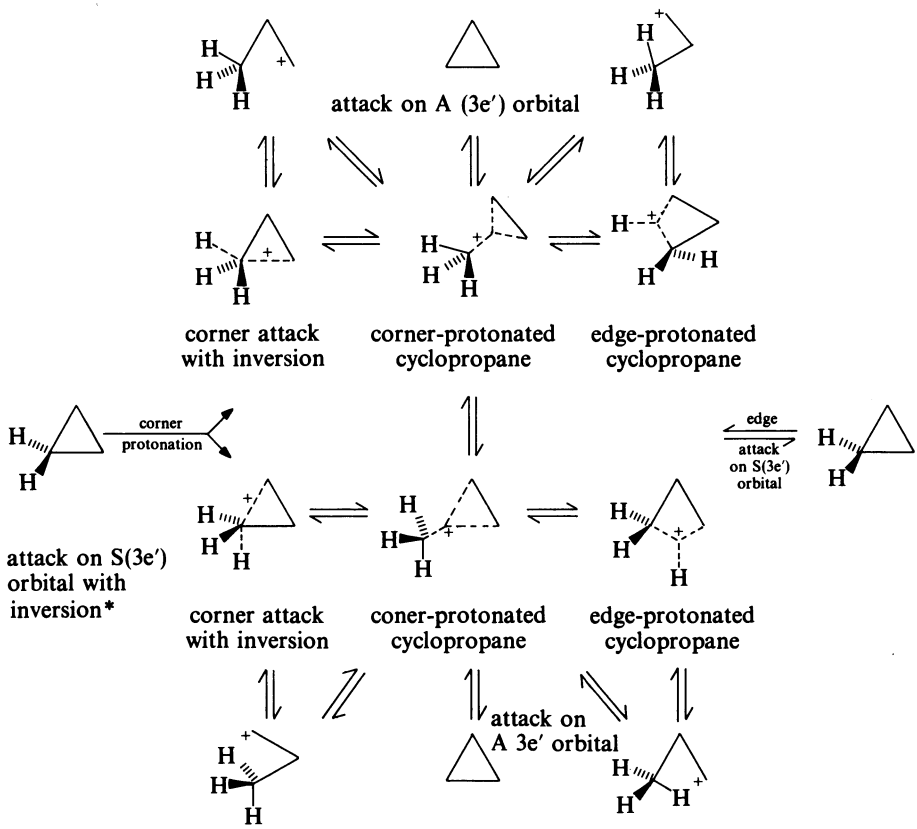
SCHEME 9

SCHEME 10

with 'corner-' and 'edge-' protonated cyclopropane although edge attack of say a 1s orbital of a proton on the S′ (3e′) orbital of cyclopropane will result in retention of configuration while corner attack on this same cyclopropane orbital results in inversion of configuration at site of attack. However, interaction of the electrophile with the *anti*-symmetric (3e′) orbital, as we have already pointed out, results in reduction of bonding of both adjacent bonds to give corner-protonated cyclopropane and the overall stereochemistry in this instance, even in the absence of rotation of the protonated carbon, depends on which of the adjacent bonds ruptures. For a sufficiently dissymmetric cyclopropane (Scheme 11) the stereochemistry of the attacking proton in the product will depend on which adjacent bond ruptures and on the relative rate of rotation of the protonated carbon with respect to rate of rupture of an adjacent bond. Sufficiently labelled substrates have not been prepared and studied to determine experimentally relative rates for these processes. The extended Scheme 12 shows the interrelation of corner and edge attack, corner-protonated cyclopropane, and also demonstrates the importance of the arguments so far developed in understanding a 1,2-methyl migration reaction. This rearrangement is of fundamental importance in organic chemistry and surprisingly relatively little detailed mechanistic study has been focused on these aspects of the migration process. Reactions in deuterated media have been observed where deuterium is not incorporated[173] in a migrated methyl, thereby excluding the intermediacy of cyclopropane, wherein deuterium is incorporated into a migrated methyl[174].



SCHEME 11



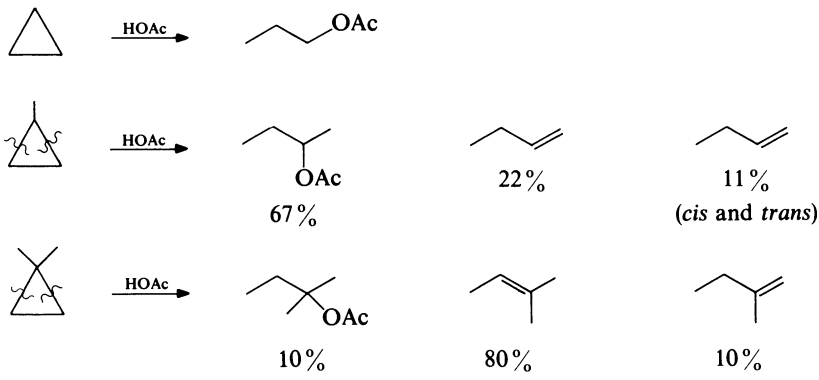
SCHEME 12. *Interaction with H 1s with degenerate HOMOs of Δ may cause lengthening of both adjacent bonds but with the bond *anti* to the proton increasing the greater.

F. Electrophilic Addition and Isomerization Reactions of Cyclopropanes

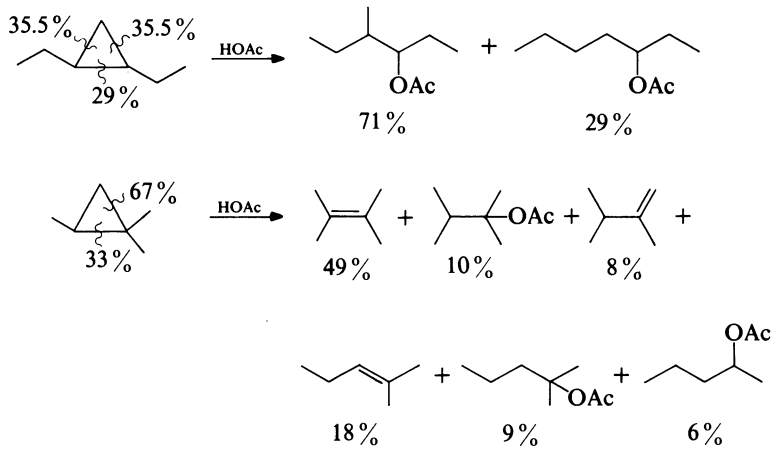
Early work has been reviewed[175–177] and we will therefore concentrate attention on the most recent work.

1. *Direction and rate of ring-opening reactions*

Acid- or electrophilic-promoted ring cleavage of a cyclopropane can be rationalized by a modified version of Markovnikov's rule which states [178] that invariably the ring opens between the carbons bearing the largest and smallest number of alkyl substituents. For cyclopropanes substituted at only one carbon the product(s) are rationalized by ring-opening to the more substituted carbocation (Scheme 13)[15]. However, with substituents on two carbons, products are generally observed of Markovnikov addition and of cleavage of the more substituted cyclopropyl σ-bond (Scheme 14)[15].

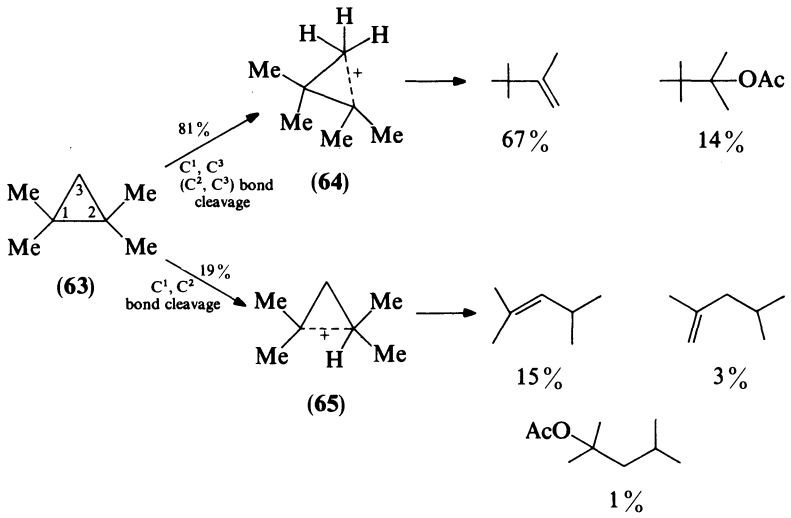


SCHEME 13



SCHEME 14

Reaction of 1,1,2,2-tetramethylcyclopropane (**63**) with acetic acid gives products of C(1), C(3) (C(2), C(3)) and C(1), C(2) bond cleavage. The comparability in calculated energy of cations **64** and **65** which presumably lie along the reaction coordinate (Scheme 15) rationalizes the observation that the electrophile does not have a strong preference for which bond is cleaved. Nevertheless, these reactions always proceed so that the nucleophile, whether from an intermolecular ($^-$OAc), or intramolecular process (H-, Me-), or if a result of fragmentation as elimination of a proton, always becomes associated with the more stable (substituted) cationic center.



SCHEME 15

The effect of substituents on the rate of reaction of cyclopropanes has been studied[15,179] (Table 7). Reactivity of cyclopropyl compounds with acid spans[15] a large range > 10^{10} (see Table 7). The rates of these reactions do not correlate with relief of strain energy, but a fair correlation was reported for log k_{rel} vs. the first vertical ionization potential (IP) for several of the hydrocarbons in Table 7. The reactions are thought[179] to involve rate determining proton transfer at a rate which depends on the ease of polarization of one (or more) of the carbon–carbon bonds. While the reaction develops toward the more stable carbocation at the product forming activated complex the structure has not relaxed to a large extent since relief of steric strain does not correlate with reaction rate. The products are considered to be formed by capture of the protonated cyclopropane before it has become an open carbocation thereby resulting in stereoselective capture by nucleophile and stereoselective hydrogen migration or loss. When the cyclopropane is in a rigid skeleton, the ability of a σ-bond to overlap with retention (*syn*-periplanar)[180] or inversion (*anti*-periplanar)[178] with the cyclopropyl bond being cleaved plays a significant role in determining the reaction course.

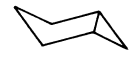
Reaction of cyclopropane with aqueous sulfuric acid results in a small amount of exchange into 'unreacted cyclopropane' and k_H/k_D for the reaction is 1.56. These observations have been interpreted as consistent with the reaction proceeding as shown in Scheme 16 where k_{-1} and k_2 have comparable values and both k_1 and k_2 are partially rate determining. In acetic acid–*p*-toluenesulfonic acid where the *p*-toluenesulfonic acid is

TABLE 7. Relative rates of acetolysis of cyclopropanes[15,179]. *Reprinted with permission from* J. Am. Chem. Soc., **107**, 1003. *Copyright* (1985) *American Chemical Society*

Compound	k_{rel}	IP
Tetracyclo[4.2.1.1^{2,5}.0^{1,6}]dodecane (**76**)	1.9×10^6	
[3.2.1]Propellane (**74**)	1.2×10^6	8.41
[4.2.1]Propellane (**75**)	93	8.50
5,5-Dimethylbicyclo[2.1.0]pentane (**78**)	79	
1,4-Dimethylbicyclo[2.1.0]pentane (**67**)	2	8.8
Bicyclo[2.1.0]pentane (**66**)	1.0	9.55
[3.3.1]Propellane (**77**)	0.36	
1,1,2,2-Tetramethylcyclopropane (**63**)	0.29	9.18
trans-Bicyclo[5.1.0]octane (**74**)	0.27	
1,1-Dimethylcyclopropane	0.065	9.72
Bicyclo[4.1.0]heptane (**69**)	0.032	9.46
cis-Bicyclo[6.1.0]nonane (**72**)	0.018	
cis-Bicyclo[5.1.0]octane (**70**)	0.017	
trans-Bicyclo[6.1.0]nonane (**73**)	0.015	
Bicyclo[3.1.0]hexane (**68**)	0.011	9.65
Methylcyclopropane	5.6×10^{-3}	10.1
Cyclopropane	4.9×10^{-5}	10.9

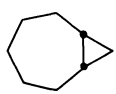
(**66**)

(**67**)

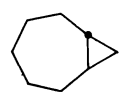


(**68**)

(**69**)



(**70**)



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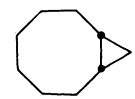
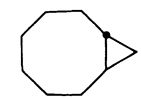
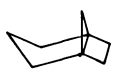


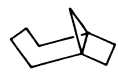
(**72**)



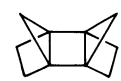
(**73**)



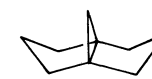
(**74**)



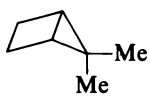
(**75**)



(**76**)



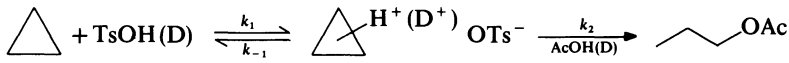
(**77**)



(**78**)

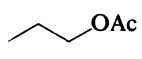
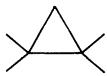
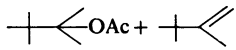
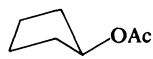
SCHEME 16

largely undissociated[181] a comparable pathway (Scheme 17) has also been proposed[15] with k_1 and k_2 again partially rate determining. Deuterium in the product, 1-acetoxypropane, is almost statistically scrambled among the three carbon atoms. For addition of deuterated acids to cyclopropanes, however, by far the majority of known reactions proceed with incorporation of a single deuterium into the product showing that k_{-1} is slow relative to product formation. For the cyclopropanes **63**, **66** and **74** which span a rate range $> 10^{10}$, $k_H/k_D = 1.4$–4.1 and k_1 is considered rate determining (Table 8).

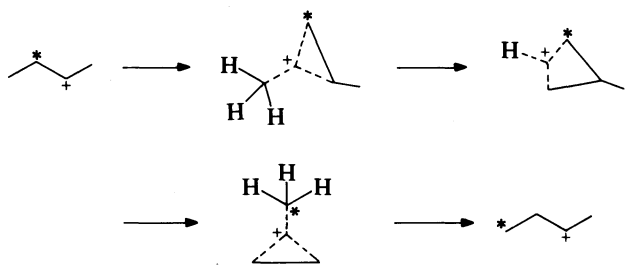


SCHEME 17

TABLE 8. Relative rates and deuterium isotope effects for acetolysis of some cyclopropanes

Cyclopropane	Products	k_H/k_D(T °C)	k_{rel}
		1.4(190)	4.9×10^{-5}
 (**63**)		3.1(60)	0.29
 (**66**)		2.9(32)	1.0
 (**74**)		4.1(25)	1.2×10^6

Protonated methylcyclopropanes are considered to be involved in the carbon scrambling of the 2-butyl cation[176,182,183] which occurs (Scheme 18) with a measured activation energy of 7.5 kcal mol^{-1}, a value in good agreement with the calculated energy difference



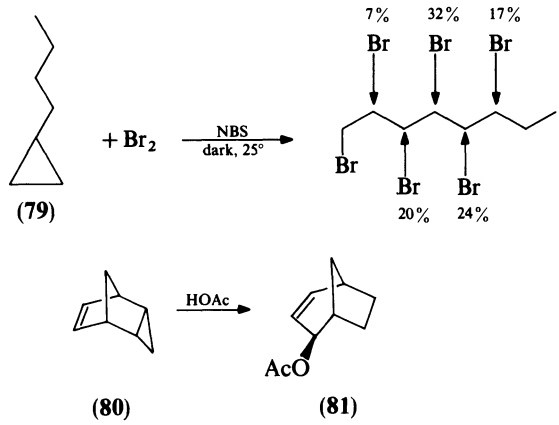
SCHEME 18

between the 2-butyl cation and edge-protonated methylcyclopropane (7.5 kcal mol^{-1}, MP3/6-31G*). The energy differences in the gas phase and in non-nucleophilic ionizing solvents have generally been found to be similar[184].

Bromine addition to cyclopropanes is slow in the absence of light unless the ring is heavily substituted[185]. In the presence of light, reaction is rapid since halogen radical attack on substituted cyclopropanes is fast even at − 78°C. In the presence of light, HBr is produced and cyclopropane reacts more competitively with proton acids than with bromine. Addition reactions to cyclopropane are generally slow in the absence of acid catalysts and therefore the conjugate acid is probably involved in reaction. The more facile reaction of cyclopropane with HBr compared with bromine is in contrast with alkene chemistry where bromine addition is the more rapid[1].

2. *Ring-opening reactions inducing molecular rearrangements*

Bromination of alkylcyclopropanes can result in extensive rearrangement[185]; bromination of *n*-butylcyclopropane (**79**) in the dark and in the presence of *N*-bromosuccinimide to trap any HBr produced, results in a mixture of 1, 2-, 1, 3-, 1,4-, 1,5- and 1,6- dibromides (Scheme 19). Rearrangement can also be induced by proton acids, for example, *endo*-tricyclo[3.2.1.$0^{2,4}$]octene (**80**) reacts with acetic acid to give 3-acetoxybicyclo[3.2.1]oct-1-enes[186] (**81**) (Scheme 19) and Djerassi and coworkers[178] have recently reported reaction of

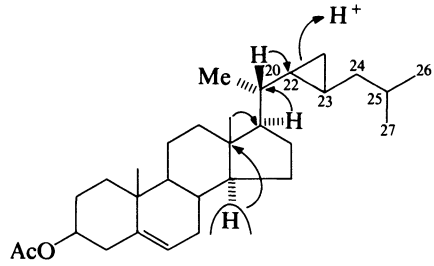


(**79**)

(**80**) (**81**)

SCHEME 19

22,23-methylenecholesteryl acetate (**82**) with trifluoroacetic acid in benzene where sequential migration of hydride and methyl groups results in partial backbone rearrangement of the steroid molecule (Scheme 20). The isolation of steroids from the marine environment which incorporate a cyclopropane ring in the side chain has led to the speculation[187] that these compounds are intermediates in biomethylation sequences[188,189]. The reaction product distribution from the isomerization of the four possible 22,23-methylenecholesterol acetates (Table 9) reflects the influence of the proximate chiral environment on the course of reaction. Competing with migration of the C(20) tertiary hydride to the site of cyclopropane bond cleavage and partial backbone rearrangement (Scheme 20) is rupture of the alternate C(23)-methylene bond and loss of a tertiary proton at C(23) or a secondary proton at C(24) to give products **91**–**99**.



SCHEME 20. Partial backbone rearrangement of 22,23-methylenecholesteryl acetate (**82**).

The stereochemical requirements for backbone rearrangement of the steroid framework have been well established[173,190–193]. From deuterium-labelling experiments, the energetics and conformational dynamics of intermediate tertiary cations for model decyl systems compared with the rate of adjacent proton loss and the role and mobility of counter ion in the reaction are known[194–197]. The mechanism for formation of the rearranged isomers **87**, **88**, **89** and **90** with both configurations at C(20) was not investigated, but epimerization at C(20) in the total backbone rearrangement of the steroid nucleus has been previously reported[198].

Reaction of the four diastereoisomers **100**–**103**[189] of the marine steroid petrosterol with trifluoroacetic acid is reported (Table 10) to give products of 1,2-methyl, 1,2-, 1,3-, and 1,5-hydride shift. The reaction course is sensitive to the relative stereochemistry between the cyclopropane ring and the adjacent chiral center at C(24). An attempt has been made to rationalize the reaction course by considering products to arise from the lowest and intermediate conformations available to the substrates. This is shown in Schemes 21 and 22 for isomers **101** and **102**. Most interestingly, deuterium-labelling experiments established that product **105** arose from a 1,5-hydride mechanism and this result suggests that the mechanism of formation of the dibromides from butylcyclopropane (Scheme 19) requires investigation.

3. Stereochemistry of reactions with electrophiles and nucleophiles

The stereochemistry of reaction of cyclopropanes with electrophilic reagents has been studied in a number of experiments[1,175–177,181,199–207]. Addition reactions to cyclopropane derivatives have been reported which proceed with retention for both electrophile and nucleophile[208,209], with inversion for electrophile and nucleophile[210], and with both retention and inversion for electrophile[211]. Reaction of cyclopropanes with bromine have been well studied[185,209,212–215]. One of the more interesting reactions is that of an ca. 85:15 mixture of *trans*- (**106**) and *cis*-cyclopropane-1,1,2,3-d_4 begun at $-78°C$ in the absence of light with a catalytic amount (0.1 equiv., cf. cyclopropane) of iron filings and completion of the reaction at room temperature for 24 hours to afford 1,3-dibromopropane as a major product[216]. The relative stereochemistry of product **107** formed by C(2)–C(3) bond cleavage has not been investigated; however, ^{1}H-NMR, investigation of product **108** showed the C(2) HD (C(3)HD) group as a doublet, $J = 7$ Hz, defining the product as *erythro* (C(2), C(3)) with a maximum height of any second doublet corresponding to 15% *threo*. Due to the symmetry of the deuterated cyclopropane, the conversion to *erythro* product **108** must result from inversion at both the site of electrophilic (corner)

TABLE 9. Isomerization products from treatment of 22,23-methylencholestenyl acetates (**83–86**) with trifluoroacetic acid in benzene[a].

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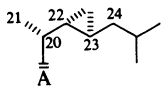
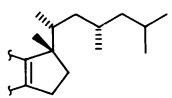
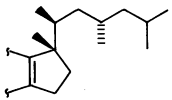
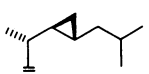
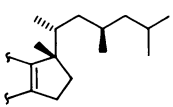
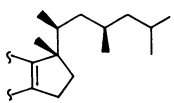
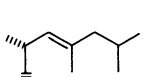
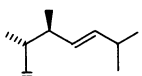
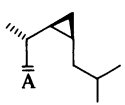
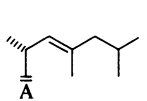
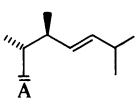
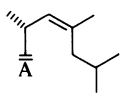
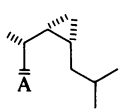
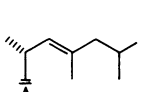
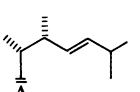
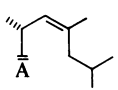
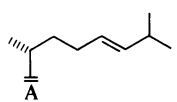
Starting materials	Backbone rearrangement		Simple ring openings			Starting material recovered	Unidentified
						27%	5%
(83)	**(87)**	**(88)**					
	14%	26%					
						38%	9%
(84)	**(89)**	**(90)**	**(91)**	**(92)**			
	6%	9%	9%	17%			
						24%	4%
(85)			**(93)**	**(94)**	**(95)**		
			16%	7%	3%		
					 	75%	8%
(86)			**(96)**	**(97)**	**(98)** **(99)**		
			5%	---	2% 1%		

[a] The difference between 100% and the sum of their percents is the yield of side-chain acetates.

TABLE 10. Product distribution following the isomerization of petrosterols (**100–104**) with trifluoroacetic acid[a]

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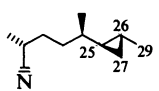
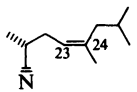
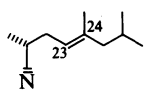
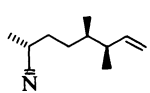
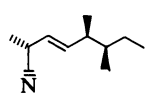
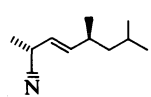
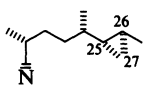
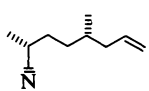
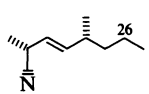
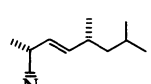
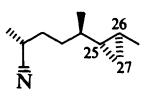
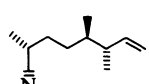
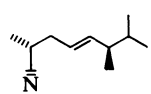
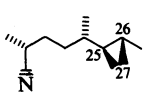
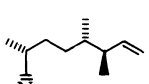
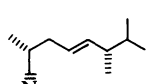
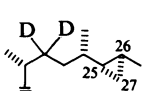
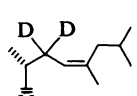
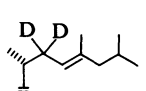
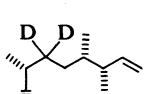
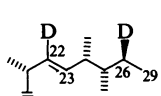
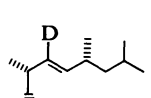
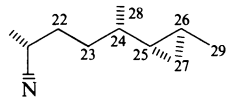
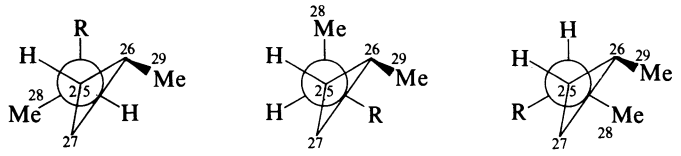
Bond-cleaved starting material	C(25)–C(27) 1,2-Hydride Shift	C(25)–C(27) 1,2-Hydride shift	C(26)–C(27) C-(29)-Proton loss	C(26)–C(27) 1,5-Hydride shift	C(25)–C(27) 1,3-Hydride shift	C(25)–C(27) 1,2-Methyl shift
 **(100)**	 4.9%	 8.1%	 14.5%	 6.8%	 2.5%	—
 **(101)**	4.2%	6.9%	 8.3%	 6.3%	 3.2%	—
 **(102)**	5.2%	11.1%	 8.6%	—	—	 10.8%
 **(103)**	5.5%	8.9%	 10.1%	—	—	 11.1%
 **(104)**						—

[a] Recovered starting material 3.5–7%; unidentified isomerization products 3–7%; the remainder of the reaction mixture consisted of hydroxy sterols which were not investigated.

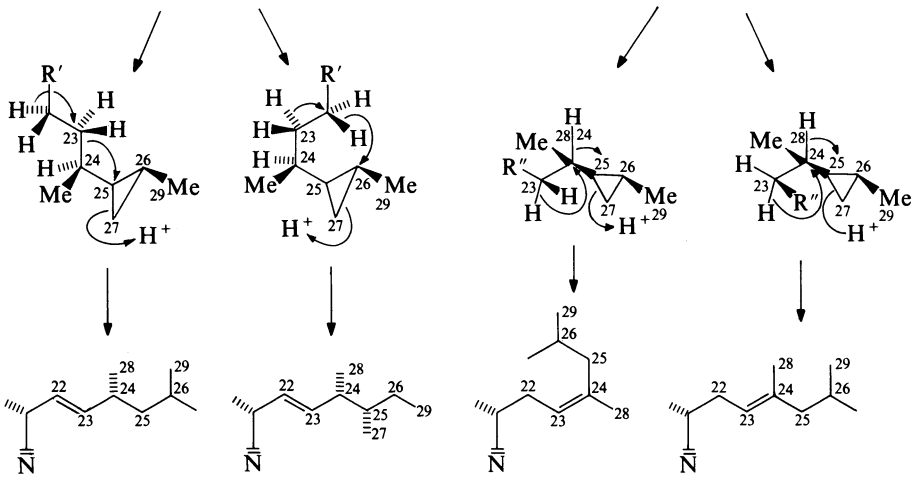


(**101**) 24S, 25S, 26S

NEWMAN PROJECTION ALONG C(24)–C(25)



lowest energy highest energy intermediate energy



(**105**)

SCHEME 21

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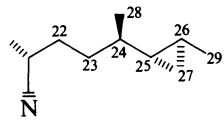
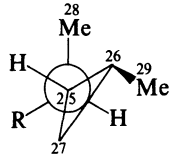
attack and also inversion at the site of nucleophilic attack (Scheme 23). Contrary to the authors'[216] conclusions, this experiment does not dictate the reaction to require a corner-brominated cyclopropane intermediate of the type **109**; in fact the experiment specifically excludes this possibility. The three equally possible corner-brominated cyclopropyl cations **110**, **111** and **112** are shown in Scheme 23 and neglecting an expected small isotope effect will be formed in the ratio 1:2:2. Cation **110** can collapse by nucleophilic attack with inversion at C(2) or C(3) to *erythro* product **108**, the stereochemistry in the product dictated by attack of nucleophile since the site of electrophilic attack is insufficiently labelled to differentiate stereochemistry. Cations **111** and **112**, ignoring the label on the pentacovalent carbon, are different conformations of the same cation and ignoring a small secondary isotope effect, should not collapse selectivity to *erythro* product **108** (the relative configuration at C(1) and C(3) of product **107** derived from attack at C(2) has not been examined). The formation of *erythro* product

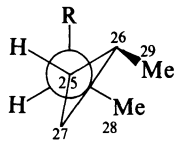


(**102**) 24R, 25S, 26S

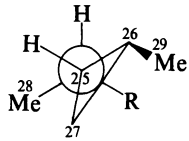
NEWMAN PROJECTION ALONG C(24)–C(25)



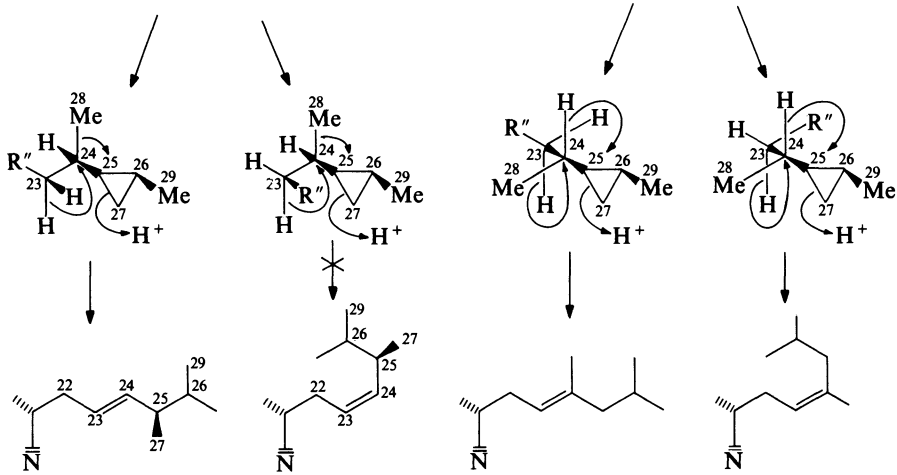
lowest energy



highest energy



intermediate energy



SCHEME 22

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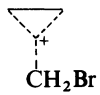
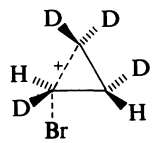
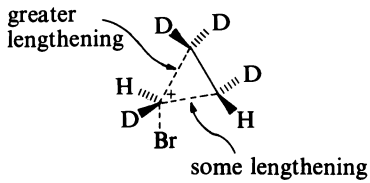


(**109**)

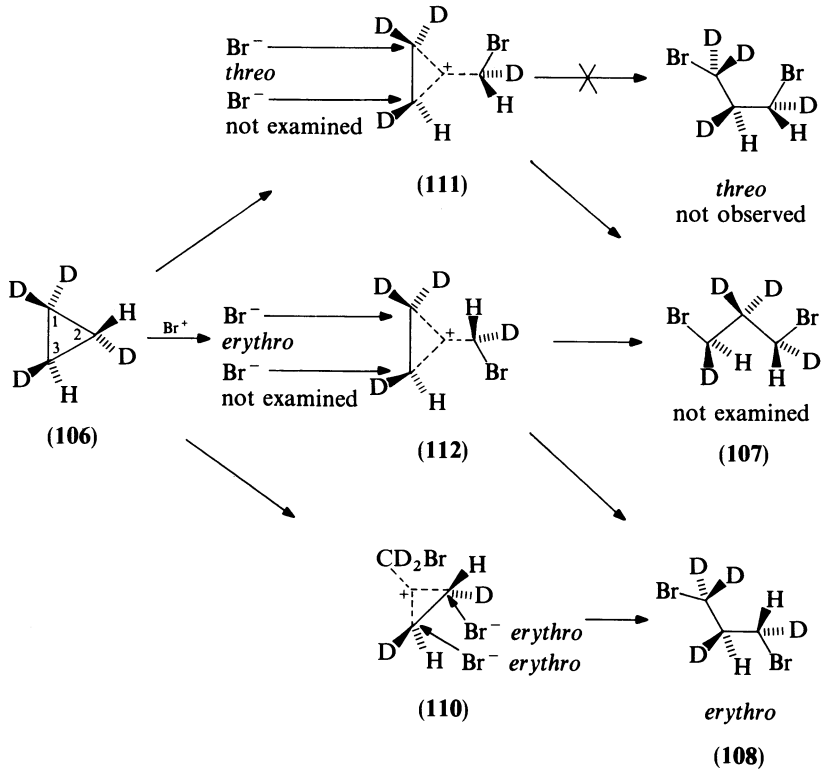


(**113**)



(**114**)

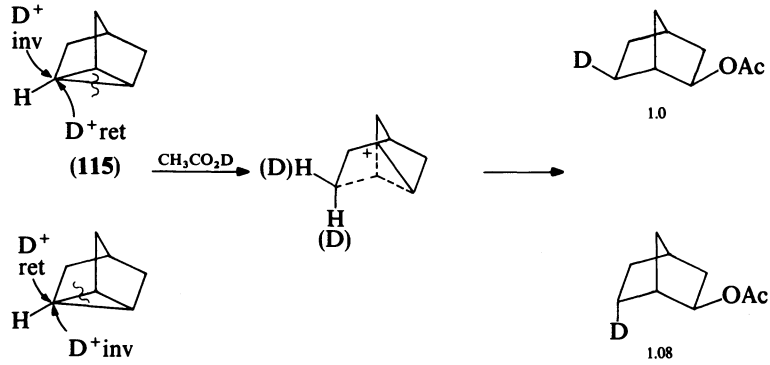
108 mitigates against intermediates **111** and **112** or requires that the stereochemistry of electrophilic attack of Br^+ to form the corner-protonated cyclopropyl cation dictate which of the adjacent carbons is attacked by nucleophile; **111** at C(3) (not examined), and due to symmetry, **112** at C(1) (observed). Such a postulate would also require rotation of the



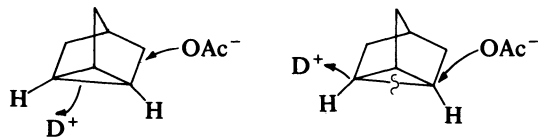
SCHEME 23

pentacoordinated carbon to be slow with respect to the rate of nucleophilic attack. Furthermore the initial structure of the brominated cyclopropane must dictate which of the adjacent sites is attacked by nucleophile. The experiment therefore excludes the intermediacy of classical corner-brominated cyclopropane **109** and dictates that the reaction proceed via a truly unsymmetrical pathway. The formation of *erythro* product **108** is consistent with the symmetric 3e′ orbital of the cyclopropane interacting with electrophile (e.g. **113**) or with a pathway analogous to that simulated by Wiberg and Kass[15] for proton attack at the corner of 1,2,3-trimethylcyclopropane where both adjacent bonds increased in length but the one on the side away from the proton increased in length more rapidly leading to inversion of configuration (e.g. **114**). An isotope effect will influence the basicity of cyclopropane at CD_2 and CHD and modify the 2:1 statistical preference for electrophilic attack at a CHD carbon as opposed to CD_2. Formation of *erythro*-dibromide **108** requires product **107** to be the *R,R*(*S,S*) dibromide, although this has not been examined.

The reaction of nortricyclene (**115**) with deuterated acid has been of considerable interest since early studies[2,17] with deuteroacetic acid were shown to give equal amounts of 6-*endo*- and *exo* (1.08 ± 0.05:1) deuteronorbornyl acetate (Scheme 24). The reaction is consistent with a symmetrical intermediate or its equivalent: a rapidly equilibrating mixture of classical ions. Alternatively, edge and corner attack (Scheme 25) are of almost



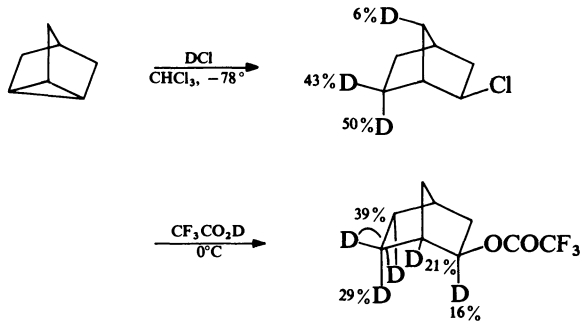
SCHEME 24



edge attack by D^+ corner attack by D^+

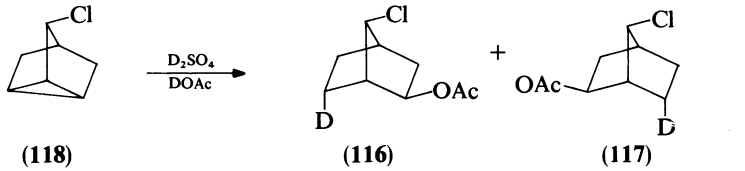
SCHEME 25

equal importance. An alternative explanation was advanced to rationalize the addition of DCl in chloroform at $-78°C$ to give the deuterium incorporation as shown in Scheme 26, namely that edge protonation occurred with substantial subsequent leakage to a non-classical or equivalent intermediate. More extensive scrambling of the label occurred with deuterated trifluoroacetic acid at 0°C[203]. A 1-methyl substituent[211] resulted in electrophilic attack in favor of retention to inversion, 3:2 respectively.

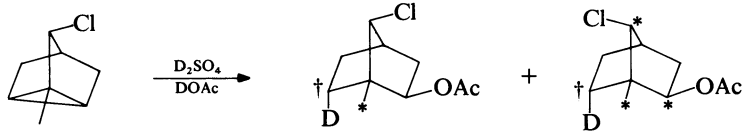


SCHEME 26

The major products **116** and **117** from reaction of 7-chloronortricyclene[218] (**118**) with D_2SO_4–DOAc comprise 70% of the reaction mixture and are consistent with edge deuteration with retention of configuration at C(6) and inversion of configuration at C(2), reaction occurring by rupture of the most basic of the cyclopropyl bonds, the bond furthest from the halogen. Reaction of 7-chloro-1-methylnortricyclene[219] with D_2SO_4–DOAc gave *syn*- and *anti*-7-chloro-2-*exo*-norbornyl acetates, **120** and **121**, where the stereochemistry of the deuterium label at C(6) was 80–90% pure *endo*. The result was interpreted as edge-cleavage of the bond most removed from the electron-withdrawing halogen.



(118) **(116)** **(117)**



(119) **(120)** **(121)**

1.04 deuterium per molecule

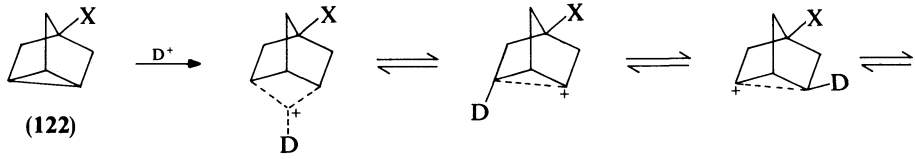
1.28 deuterium per molecule

* sites of additional deuterium incorporation
† 80–90% stereochemically pure *endo*

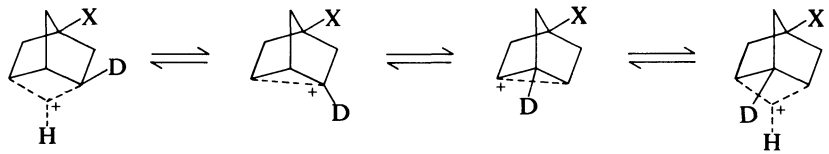
The symmetrical nortricyclenes (**122**)[204] where the substituent does not sterically hinder the front face of the molecular system have been reacted with deuterosulfuric acid in acetic acid-d_4 and the stereochemistry of the incorporated deuterium at C(6) found to vary with substituent; *endo*-deuteration increasing from X = H to X = I. The importance of 6,2-hydride shift decreased from 14.3 ± 1.0% for X = H to 6.0 ± 1.1%, 6.4 ± 0.5 and 8.1 ± 0.7 for X = Cl, Br and I respectively. If cleavage of the cyclopropane involved a symmetrical ion (or its equivalent) (e.g. **123, 124** or **125**) then the *exo* and *endo* ratio at C(6) would be unaffected by the substituent but if unsymmetrical (e.g. **126, 127**) the rate of rearrangement could be affected by the mass of the substituent, a ponderal effect[220], or a polar effect. Werstiuk and coworkers[219] considered the results above to be best rationalized by a mechanism (Scheme 27) which involves formation of a rapidly equilibrating 6,2-bridged norbornyl cation. They conclude that while edge-protonated nortricyclenes can be involved as intermediates in the reaction, the simplest cleavage mechanism involves edge-wise approach of D^+ to the cyclopropyl bond with a corner slide to generate an unsymmetrical 6,2-bridged cation.

Reaction of the all *cis*-1,2,3-trimethylcyclopropane with deuteroacetic acid[200] gives product with 68% retention of configuration at the site of electrophilic attack and 32% inversion, corresponding to 68% edge: 32% corner attack of electrophile. The nucleophile attacks with greater than 95% inversion. Calculations by Wiberg[15] for this specific system show a comparable energy surface for both configurations of attack.

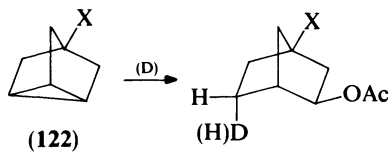
A study of the products from reaction of bicyclo[2.1.0]pentane with HOAc (Scheme 28) and HOAc/TsOH (Scheme 29) and the analogously labelled acids is complex[221] and has



(122)

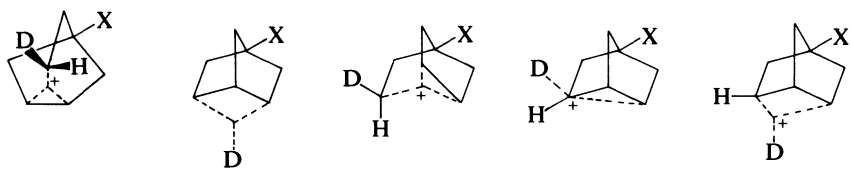


SCHEME 27



(122)

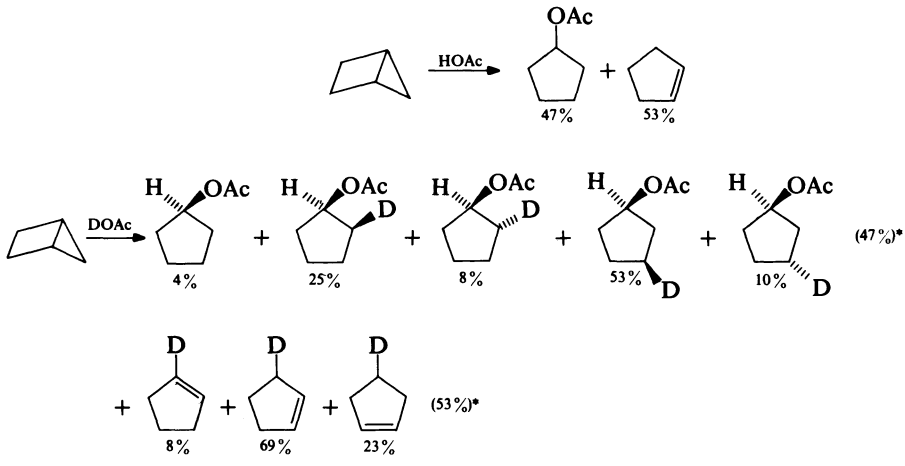
	C(6) *endo*:*exo* D	excess % C(6)*endo*-D	%D at C(1) and C(2)		%6,2-hydride shift
X=H	1.09±0.02	4.6	7.5±0.6	6.8±0.4	14.3±1%
Cl	1.30±0.03	14.9	2.9±0.5	3.1±0.6	6.0±1.1%
Br	1.40±0.04	21.4	3.4±0.4	3.0±0.1	6.4+0.5%
I	1.45±0.05	22.5	3.9±0.4	4.2±0.3	8.1±0.7%



(123) (124) (125) (126) (127)

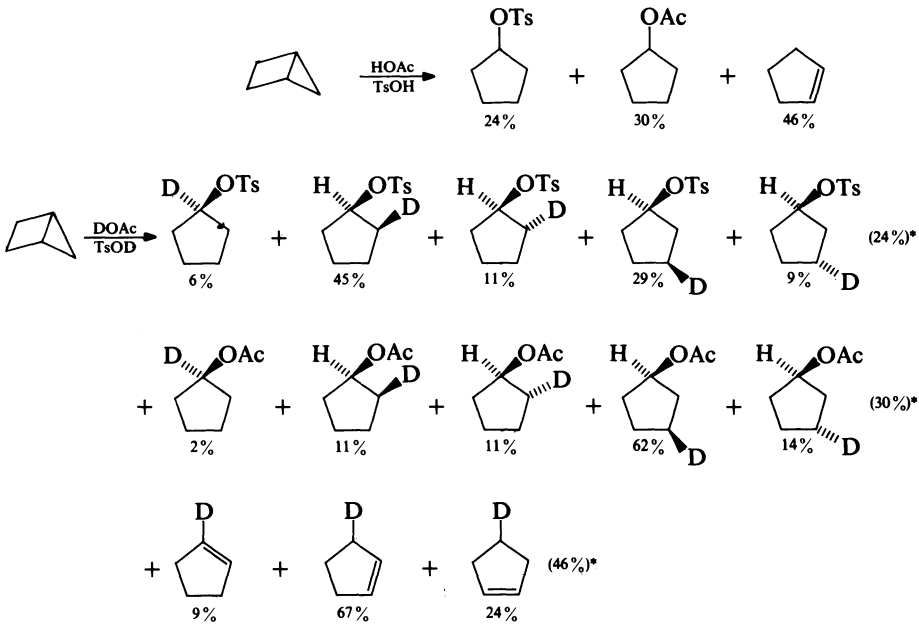
symmetrical intermediates unsymmetrical

been analyzed to show that cyclopentyl acetate is formed in a process involving inversion at C(1) and C(4) while the cyclopentyl tosylate is formed largely by a process involving inversion at the site of proton attack, migration of the *endo*-5-proton and capture of the tosylate anion (Scheme 30). The intermediacy of an open cyclopentyl cation is excluded. Calculations show the C(1)-protonated species to have a lower energy than protonation at C(5), relieving considerable strain by stretching the central bond and accounting for preferential cleavage of the central bond. The reaction is envisaged to proceed by initial formation of ion pair **128** which will collapse to form *cis*-3-deuterio tosylate (**129**), undergo an *endo*-5 hydrogen shift followed by collapse to give *cis*-2-deutero tosylate (**130**),



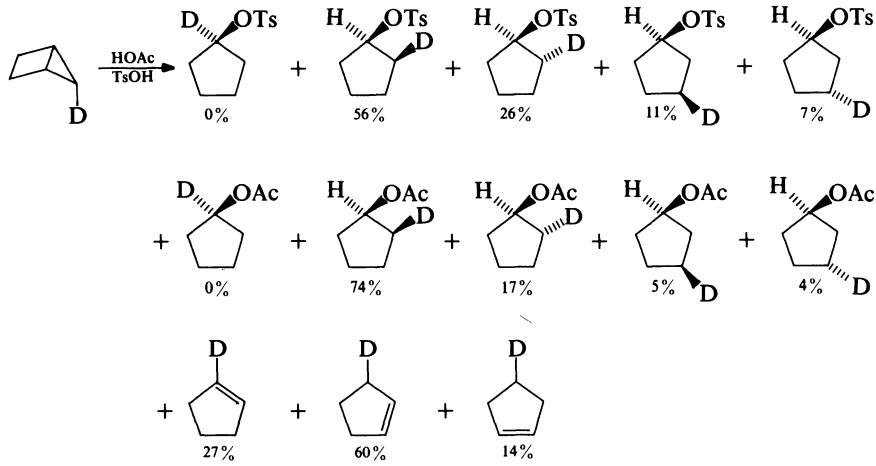
*percent of total product

SCHEME 28



* percent of total product

SCHEME 29. *Continued.*



SCHEME 29

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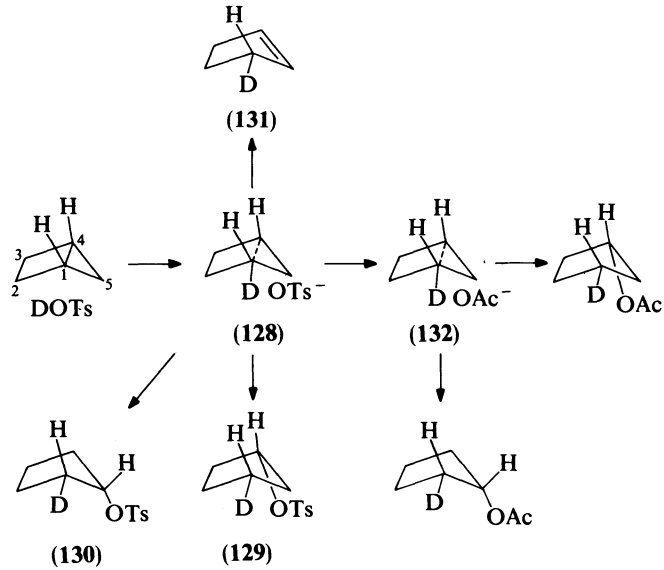

SCHEME 30

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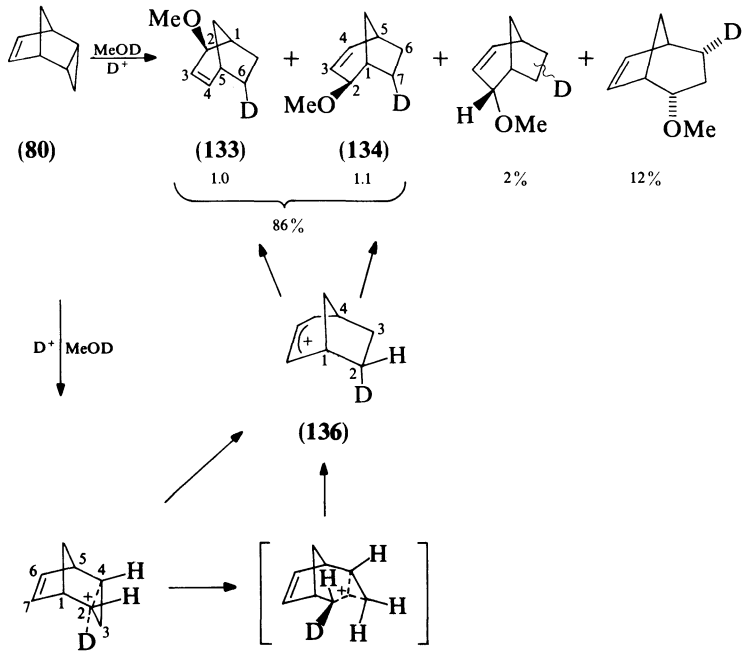
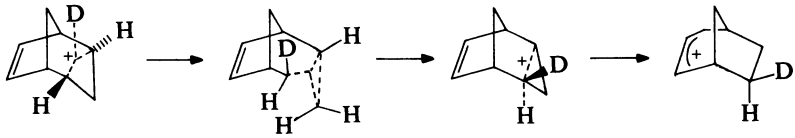
lose the *endo*-5 proton to give cyclopentene (**131**), or undergo ion pair exchange to give the acetate ion pair (**132**) which can undergo analogous reactions.

Reaction of *endo*-tricyclo[3.2.1.$0^{2,4}$]oct-6-ene (**80**) with acidified methanol-O-d^{180,202} causes rupture of the most substituted cyclopropyl σ-bond (Scheme 31). The mode and stereochemistry of proton (deuteron) attack, corner (inversion) vs. edge (retention) at the strained C(2)–C(4) cyclopropyl σ-bond can be distinguished by determination of the stereochemistry in the product. The major product is a mixture of 6-*endo*-deutero-2- and 7-*endo*-deutero-2-*exo*-methoxybicyclo[3.2.1]oct-3-ene, **133** and **134** respectively, establishing that electrophilic attack in the acid-catalyzed opening of the cyclopropane moiety occurs with inversion of configuration. This corner attack of electrophile is not to be confused with or regarded as requiring the intermediacy of a corner-protonated cyclopropane(**135**). A corner-protonated cyclopropane would involve weakening of both the C(2)–C(4) and C(2)–C(3) σ-bond with charge development at both C(3), a primary carbon, and C(4), a secondary carbon. The memory effect in favor of deuterium at C(7), cf. C(6), suggests that C(4) of the allylic cation(**136**) from which C(8) has migrated is marginally hindered relative to C(2). The stereochemistry of deuterium in the major product precludes edge attack on the C(2)–C(3) bond of the alkene and reorganization to the corner-protonated species in the reaction since such a process would require *exo*-deuterium in the product (Scheme 32). The stereochemistry and labelling results are accounted for in this reaction as shown in Scheme 31. There is no need to include edge protonation of cyclopropane or a corner-protonated cyclopropane intermediate. The



SCHEME 31



SCHEME 32

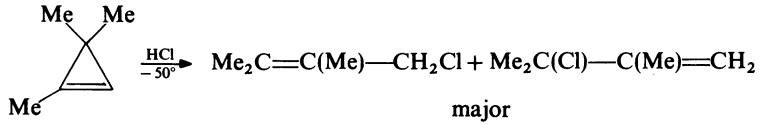
reaction proceeds by electrophilic attack at the corner of the cyclopropane ring and involves the intermediacy of an allylic cation (**136**) and a small memory effect.

The results of these studies indicate the need for caution in making generalizations concerning the stereochemistry of electrophilic attack at cyclopropane.

G. Acid-catalyzed Rearrangements of Cyclopropenes

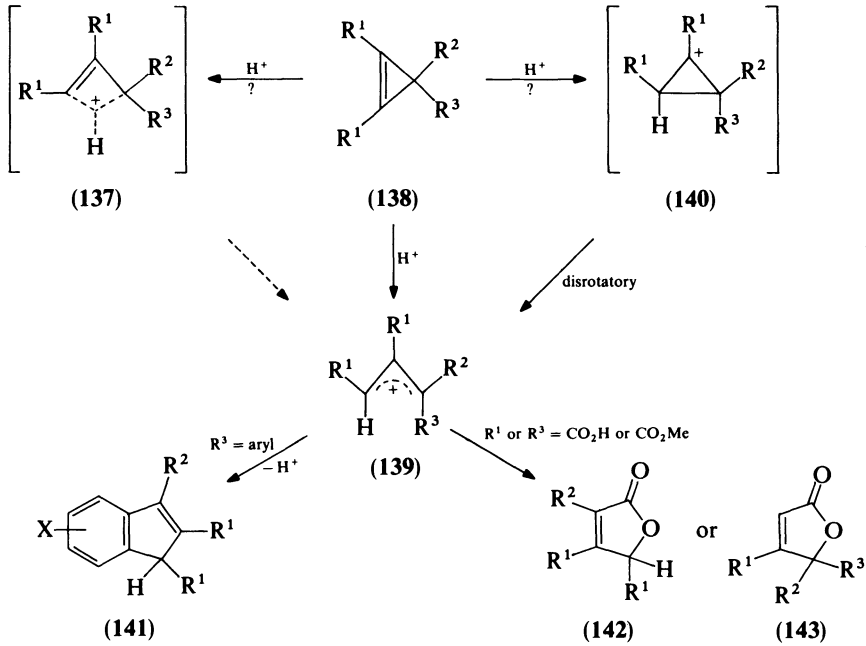
Literature dealing with the electrophilic ring-opening of cyclopropenes is sparse in relation to that for the saturated analogs. The earliest review by Closs[67] and that by Halton and Banwell (this volume) are noteworthy. The reader is referred to these reviews for more comprehensive coverage.

The basicity of cyclopropenes (or methylenecyclopropanes) is almost certainly associated with the π-bond on the basis of orbital energies (photoelectron spectroscopy)[222] and frontier orbital considerations[102]. Closs[67] has considered the possibility of an edge-protonated cyclopropene (**137**) (Scheme 33) as an intermediate in the acid-catalyzed ring-opening isomerizations of cyclopropenes (**138**); however, evidence supporting this suggestion has not been forthcoming. While the allylic cation(**139**) is generally accepted as a requisite intermediate in these rearrangements, it is still unclear if ring-opening (disrotatory?) is synchronous with cyclopropene protonation or if cyclopropyl cation(**140**) is actually a prior intermediate. The observed[67] regiospecific ring-opening addition of anhydrous HCl to 1,3,3-trimethylcyclopropene at $-50°C$ is at least consistent with the latter alternative.



When the presumed intermediate allylic ion **139** (Scheme 33) carries an aryl group on a terminal carbon, e.g. R^3 = aryl, cyclization occurs to yield the indene(s) **141**. Examples include the formation of indenes **141a**,[223] **141b**,[224] **141c**,[224] and **141d,e**[224] from acid-catalyzed rearrangement of their respective cyclopropenes(**138**). Similarly, lactonization results if R^1 or R^3 in ion **139** is a carboxylic acid or carboalkoxy group. Thus, diphenylcrotonolactone (**142**) (R^1 = Ph; R^2 = H) is formed in good yield on heating 2,3-diphenylcyclopropene carboxylic acid at or above its melting point[225], whereas the analogous crotonolactone **143** ($R^1 = CO_2Me$; $R^2 = R^3$ = Ph) is produced upon simply heating dimethyl 3,3-diphenyl-1,2-cyclopropene dicarboxylate in aqueous acetic acid.[226].

Related metal ion-catalyzed (e.g. Ag^+, Hg^{2+}, Pd^{2+}) rearrangements of cyclopropenes provide analogous ring-opened products; however, the mechanistic aspects are more complicated and beyond the scope of this review.



a, $R^1 = R^3 = Ph$; $R^2 = X = H$
b, $R^1 = R^2 = Ph$; $X = H$
c, $R^1 = Ph$; R^2 = mesityl; $X = H$
d, $R^1 = Ph$; R^2 = *p*-anisyl; $X = H$
e, $R^1 = R^2 = Ph$; $X = OMe$

SCHEME 33

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CHAPTER 7

Preparation of cyclopropyl derivatives

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I. INTRODUCTION

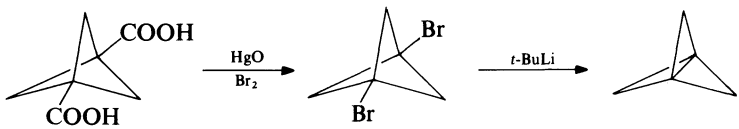
In 1971, an excellent, comprehensive review on the synthesis of cyclopropyl compounds was given by Wendisch[1]. However, the advancement of synthetic methodologies in organic chemistry in recent decades is extremely rapid, and the preparative methods of the cyclopropyl derivatives are not an exception. Accordingly, it may be appropriate to summarize the recent advancements in the synthesis of three membered carbocycles on this occasion. In the present review, we aim to emphasize the synthetic procedures which have been developed in the last fifteen years up to 1984. Since a comprehensive coverage of the literature would be far beyond the space allotted here, citations are limited to the reactions suggesting new synthetic aspects. Numerous examples demonstrating the applications of the various reactions for the synthesis of certain specific compounds are usually not quoted. In particular, some types of reactions are merely mentioned by referring to recent review articles.

This review is divided into four sections; namely, 1,3-bond formation, combination of C_2 and C_1 building blocks, rearrangement reactions, and transformations of cyclopropyl derivatives. Aside from the present chapter, there are other chapters (8, 9, 17, 19–23), in which additional information may be found. The readers who are interested in the synthesis of some specific compounds are therefore requested to refer not only to the list of contents of the present chapter, but also to the related chapters.

II. 1,3-BOND FORMATION

A. 1,3-Elimination of Two Heteroatoms

The synthesis of cyclopropyl compounds by reductive 1,3-elimination of two heteroatoms has been carried out by employing metallic as well as organometallic reagents as the reducing agent. Wurtz-type reactions are frequently employed and, in the reactions of 1,3-dibromides and 1,3-diiodides, Zn[2,3], Na[4], Mg[5,6], Li(Hg)[7], Cr(II)[8], LAH[9], $RMgX/FeCl_3$[10] and RLi[11–14] (e.g., equation 1)[12] have been used. In the preparation of highly strained propellanes, 1,3-dibromides have been treated with potassium in the vapor phase[15]. In the reactions of dichlorides, Cr(II), Li and Na have been used as the reducing agent, but 1,3-dichlorides are less satisfactory than 1,3-dibromides for carrying out the reaction[16]. An addition of sodium iodide may complement the relatively low reactivity of

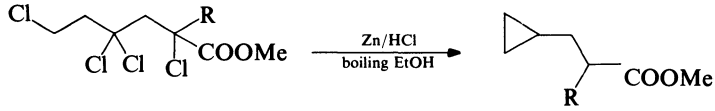


(1)

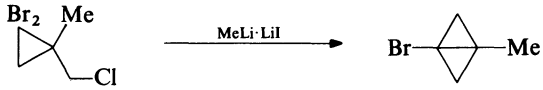
the chlorides[17]. Primary halides usually give satisfactory results, whereas secondary and, in particular, tertiary halides tend to produce olefinic side products arising from the β-

elimination of HX. When Zn is used as the reducing agent, a zinc halide-promoted rearrangement may complicate the reaction, but this side reaction is suppressed by addition of EDTA[3]. It has been shown that the configuration of the halides is important in the reaction of bicyclic systems under certain reaction conditions[18, 19].

Polychloroalkanes, represented by $CCl_3CH_2C(Cl)\ R^1R^2$ and $RCCl_2CH_2C(Cl)\ R^1R^2$, which are readily prepared by reaction of alkenes with CCl_4 or $RCCl_3$, undergo simultaneous cyclization and hydrogenolysis to give alkylcyclopropanes in the treatment with Zn/EtOH/HCl (equation 2)[16, 20]. The reactions of compounds possessing a $-CCl_2CH_2CCl_2-$ moiety with Zn/DMF afford cyclopropenes[21]. Halocyclopropanes



(2)

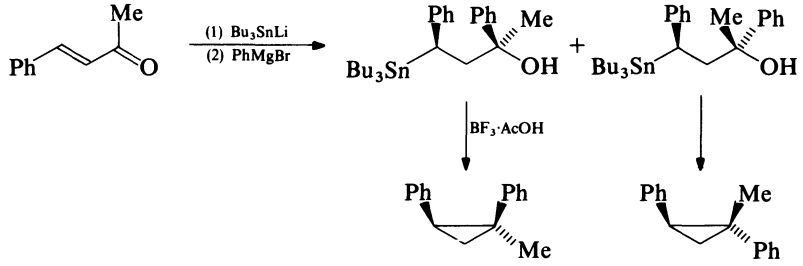


(3)

including 1-halobicyclo[1.1.0]butanes have been obtained in the reaction of 1,1,3-trihalo derivatives with MeLi·LiI (equation 3)[13]. Debromination of α,α′-dibromoketone acetals with Mg or Zn affords cyclopropanone acetals in satisfactory yields, although β-elimination giving allenes may compete with the cyclization[22]. The addition of Grignard reagents to 1,3-dichloro-2-propanone, followed by the treatment of the adduct with Li, produces 1-substituted cyclopropanols[23]. A 1,3-elimination of a halogen and an alkoxyl group giving three-membered ring products has been reported in a few cases[5, 14]. Cyclization of 1,3-diols with low-valent titanium reagents has so far been successful only for benzylic derivatives[24].

The 1,3-bond formation by electrolysis has been successfully applied for 1,3-disulfonates [25] and 3-phenylthio-1-sulfonates[26] as well as 1,3-dihalides[27]. The electrolysis of α,α′-dibromoketones in the presence of nucleophiles gives cyclopropanol derivatives resulting from the addition of the nucleophile to the carbonyl group[28]. The electrolytic cyclization of 1,3-dibromides has been shown to be non-stereospecific[29].

3-Trialkylstannyl derivatives readily cyclize to three-membered ring products by replacement of the stannyl group under conditions of 3-stannylalkyl cation formation[30–32]. It has been shown that the cyclization proceeds stereospecifically with inversion of configuration at both reaction centers (equation 4)[32]. The precursors for this reaction

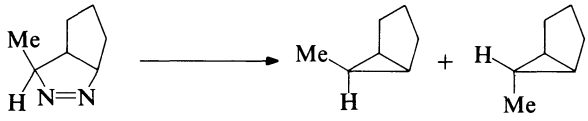


(4)

may be prepared by Michael addition of trialkylstannyllithium to α,β-unsaturated carbonyl compounds[32].

B. Extrusion Reactions

The nitrogen extrusion from 1-pyrazolines and 3*H*-pyrazoles giving cyclopropanes and cyclopropenes, respectively, has been extensively reviewed[33-37]. The cyclopropane synthesis from 1-pyrazolines can be executed thermally as well as photochemically, but the latter method generally gives substantially better results than the former. The major side reaction observed in the thermal process is the production of olefins, which arise in the migration of a substituent from the C(4) to C(3) position. A retro-1,3-dipolar addition producing a diazoalkane and an olefin has been observed in certain cases. The decomposition of 3-acyl- or 3-alkoxycarbonyl-1-pyrazolines is catalyzed by acids, such as perchloric acid[38] and boron trifluoride[39] and by Ce (IV)[40,41]. The stereochemical course of the deazetation of 1-pyrazolines has been extensively investigated in connection with studies related to the chemical behavior of 1,3-biradicals[34,42]. The thermal decomposition of 3,5-dialkyl-1-pyrazolines proceeds with predominant single inversion of stereochemistry[43]. The direct photolysis tends to give the cyclopropanes with retention of relative stereochemistry of the starting pyrazolines. The triplet sensitized decomposition, in contrast, generally leads to an extensive loss of the stereochemistry, but it often gives better yields of the three-membered ring products than those obtained in the direct photolysis (equation 5)[34,42].

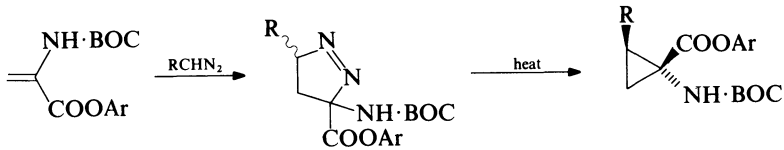


(5)

Thermolysis (260 °C)	21%	67%
Direct *hv*	61%	30%
Sensitized *hv* ($Ph_2C=O$)	41%	59%

The photochemical nitrogen extrusion from 3*H*-pyrazoles provides a major access to cyclopropenes. It has been shown that the 3*H*-pyrazoles are transformed into diazoalkenes in the first step of the decomposition, and the resultant diazoalkenes give the cyclopropenes by loss of nitrogen[44]. Benzocyclopropenes have been prepared in a similar manner[45]. The thermal or photochemical decomposition of 4-alkylidene-1-pyrazolines produces methylenecyclopropanes[46]. The products obtained especially in the triplet sensitized photolysis are frequently derived by a methylenecyclopropane rearrangement.

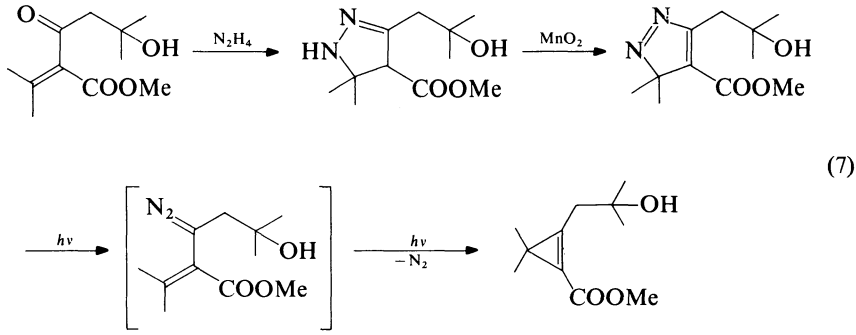
1-pyrazolines and 3*H*-pyrazoles are commonly prepared by a 1,3-dipolar cycloaddition of a diazo compound to an olefinic substrate (Section III.D). Cyclopropanations via pyrazolines are particularly valuable for the synthesis of alkylcyclopropanes, since the direct carbene route (Section III.A.2) is virtually impractical due to rapid intramolecular insertion of alkylcarbenes. Thus, many alkylcyclopropanes (cf. equation 6)[47,48] including highly strained bicyclo[1.1.0]butanes[49] and bicyclo[2.1.0]pentanes[50] have been prepared in this way. Optically active cyclopropanes have also been obtained in the reaction of chiral olefinic substrates with diazoalkanes via the 1-pyrazolines[41,51].



(6)

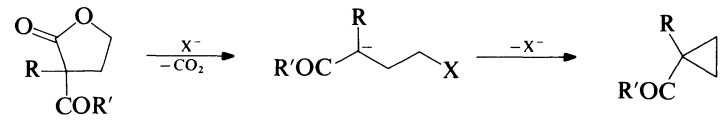
BOC = COOBu-*t*; Ar = *p*-$NO_2C_6H_4$; R = H, Me, Et, *i*-Pr, Ph

1-Pyrazolines can also be prepared by the oxidation of pyrazolidines[52]. 2-Pyrazolines, which are readily obtained in the reaction of α,β-unsaturated ketones with hydrazine, also undergo nitrogen extrusion at elevated temperature usually in the presence of a basic catalyst[53]. The reaction is believed to proceed via 1-pyrazolines. Treatment of 3,3,5-trialkyl-2-pyrazolines with lead tetraacetate followed by thermolysis affords cyclopropyl acetates[54]. Oxidation of certain 2-pyrazolines with manganese dioxide gives 3*H*-pyrazoles, which in turn produce cyclopropenes in the photolysis (equation 7)[55].



(7)

Extrusion of carbon dioxide to give cyclopropyl ketones has been observed in the treatment of 2-acylbutanolides with a halide salt in DMSO or DMF (equation 8)[56]. 4-Aryl-or 4-alkenylbutenolides also expel CO_2 photochemically[57]. Irradiation of cyclobutanones with UV light often gives cyclopropanes by loss of carbon monoxide[58]. In this

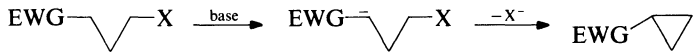


(8)

photoreaction, however, the fragmentation of the cyclobutanones to give alkenes and ketenes, as well as the ring expansion to produce five-membered oxacarbenes, can compete with the CO ejection. The relative effectiveness of the cyclopropane formation is markedly dependent on the nature of the substituents on the cyclobutanone and on the photolysis conditions. Certain thietane-1-oxides[59], thietane-1,1-dioxides[60] and cyclic sulfinate esters[61] have also been shown to undergo extrusions of sulfur oxide or sulfur dioxide to give cyclopropyl derivatives.

C. 1,3-Elimination of HX; Intramolecular Displacement Reactions

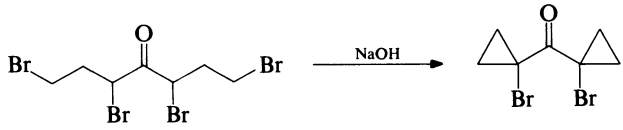
A wide variety of active methylene and methyne compounds substituted by a leaving group (X) at the γ-carbon atom undergo 1,3-elimination of HX to give cyclopropyl derivatives (equation 9). This type of cyclization has successfully been executed in the



(9)

EWG = electron-withdrawing group

compounds ranging from strongly activated carbonyl (e.g., equation 10)[11,62-64], cyano[65,66]and sulfonyl[67,68]derivatives to moderately activated 1-alkenyl[69], 1-alkynyl[70],

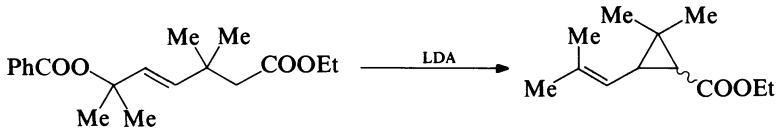


(10)

aryl[71], pyridyl[72], thienyl[73], and phenylthio[74, 75] derivatives. As to the leaving group (X), frequently used functions are halogens, sulfonyloxyls, and acyloxyls. Oxirane and oxetane ring systems can also serve as the X part. The cyclization step is regarded as an intramolecular S_N2 displacement, and hence the cyclopropane formation generally proceeds with inversion of configuration at the carbon bearing the leaving group.

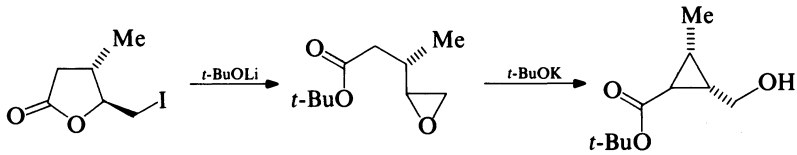
The synthesis of highly strained compounds, such as bicyclo[1.1.0]butanes[76, 77], bicyclo[2.1.0]pentanes[78] and tricyclo[3.1.0.$0^{2,4}$]hexanes[79] has been achieved by the application of this type of reaction. Even bromocyclopropanes, where the bromine usually resists displacement by nucleophiles, undergo such an intramolecular substitution. In this manner, spiropentane derivatives have been prepared[80]. Vinylogous activation as well as vinylogous substitution has also been accomplished in several cases. Thus, β-cyclopropyl-α,β-unsaturated carbonyl compounds have been obtained in the reaction of conjugated enones bearing the leaving group at the ε-carbon atom (equation 11)[81] and a variety of γ,δ-unsaturated carbonyl compounds have provided 2-(1-alkenyl)-cyclopropyl derivatives (equation 12)[82].

(11)



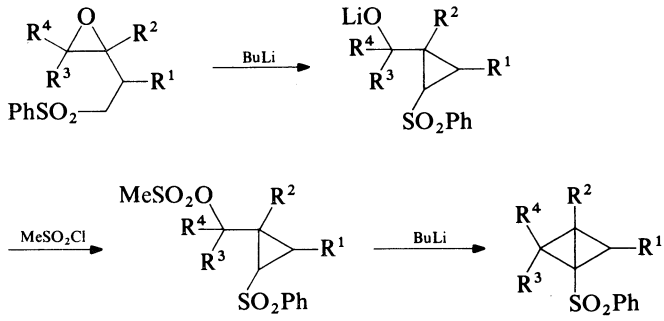
(12)

In an analogous manner, treatment of 4-(2-haloethyl)-phenols[83] and -1-naphthols[84] with bases produces spiro[2.5]octa-4,7-dien-6-ones and their benzo analogues, respectively. The basic treatments of β-oxiranyl ketones[63], esters (equation 13)[64], nitriles[66], sulfones[68] and alkynes[70] affords 2-(hydroxymethyl) cyclopropyl derivatives, usually as the sole cyclization product. The cyclization occurs regiospecifically by the intramolecular attack of the anion on the γ-carbon in the oxirane ring. Attack of the anion on the δ-carbon in the oxirane, which should lead to the formation of cyclobutanols, usually does not take



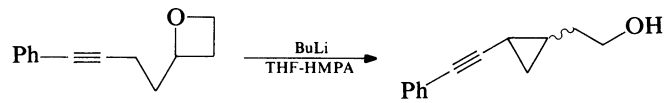
(13)

place. 2-(Hydroxymethyl)cyclopropyl sulfones obtained in the reaction of 2-oxiranyl sulfones have been further transformed into 1-sulfonylbicyclo[1.1.0]butanes by the successive treatments of the cyclopropyl sulfones with methanesulfonyl chloride and alkyllithium (equation 14)[77]. Even relatively low reactive oxetane rings undergo the



(14)

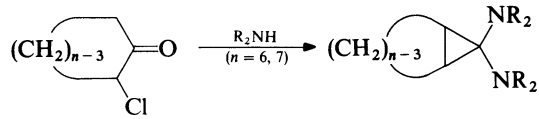
intramolecular displacement to give 2-(2-hydroxyethyl) cyclopropyl derivatives. Examples are the reactions of 2-(2-oxetanyl)ethylarenes, -alkenes, and -alkynes with alkyllithium (equation 15)[71].



(15)

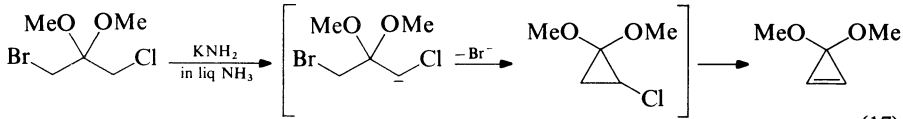
trans/*cis* = 3

Sterically crowded α-haloketones[85] and α-haloketimines[86] cyclize to cyclopropanones and ketimines, respectively, upon treatment with bases. The reaction of a series of α-haloketones with dialkyl sodiomalonate has been found to give the adducts of the malonate anion to incipient cyclopropanones, i.e. (1-hydroxycyclopropyl)malonic esters, instead of the products of the Favorskii rearrangement[87]. Cyclopropanone aminals[88] and 1-alkoxycyclopropylamines[89] have been obtained in the reactions of cyclic α-chloroketones (equation 16) with secondary amines and of α-chloroketimines with



(16)

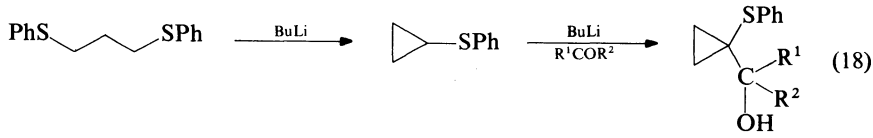
alcohol/base, respectively. α,α'-Dihaloketones afford substituted cyclopropenones by successive 1,3- and 1,2-eliminations[90]. In a seemingly analogous manner, the reaction of α-bromo-α'-chloroacetone dimethyl acetal with potassium amide in liquid ammonia provides cyclopropenone dimethyl acetal (equation 17)[91]. The 1,3-elimination of hydrogen bromide can effectively compete with the 1,2-elimination of methanol.



(17)

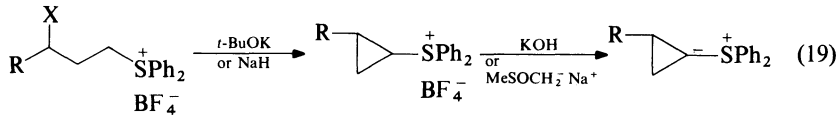
Sulfur and selenium substituents can serve both as the activating group and as the leaving group. Thus, thio-[92] and selenoacetals[93] of aldehydes bearing a leaving group on the β-carbon atom readily afford cyclopropanone thio- and selenoacetals, respectively. 1,3-Bis (phenylthio) propanes[75] as well as 3-halopropyl sulfides[74] provide cyclopropyl sulfides

(equation 18). Treatment of 5-(phenylthio)alkenes with BuLi/TMEDA produces 1-alkenylcyclopropanes[69].



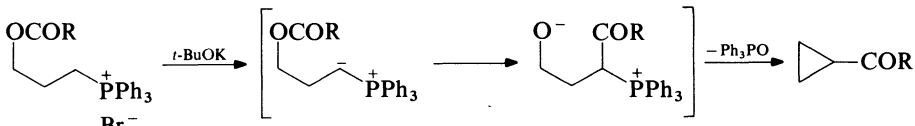
(18)

Cyclization of γ-substituted phosphonium[94] and sulfonium[95] salts by 1,3-elimination followed by proton abstraction affords the corresponding cyclopropyl ylides



(19)

(equation 19). The ylides are valuable for the synthesis of various functionalized compounds[96, 97]. Treatment of 3-acyloxypropyl phosphonium salts with base directly gives acylcyclopropanes. The reaction has been proposed to proceed as in equation 20[98]. Certain



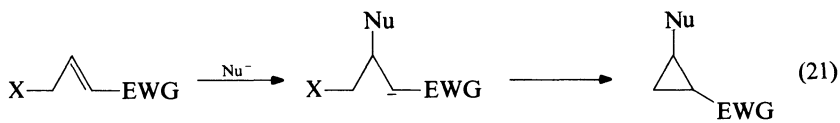
(20)

4-thiacyclohexene and 1,3-butadienyl sulfide derivatives give 2-cyclopropylvinyl sulfides when treated with alkyllithium[99]. The reaction proceeds via 4-thiacyclohex-2-enide anions. The formation of 2-cyclopropylphenol from the hydrazone of 4-chromanone may proceed analogously[100].

D. Cyclization of Allylic Derivatives

1. γ-Substituted Michael acceptors and nucleophiles

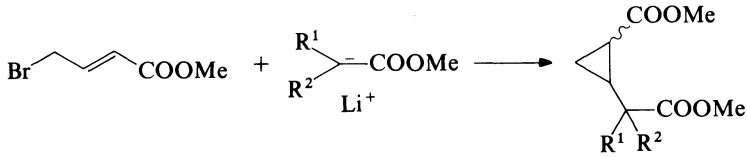
The Michael addition of nucleophiles to acceptors in which the γ-carbon atom is substituted by a leaving group generates intermediates which are capable of undergoing an intramolecular displacement to give three-membered ring products. In this way, a variety of cyclopropyl compounds carrying electron-withdrawing group(s) (EWG) have been prepared (equation 21). The γ-substituted Michael acceptors are, however, bidentate



(21)

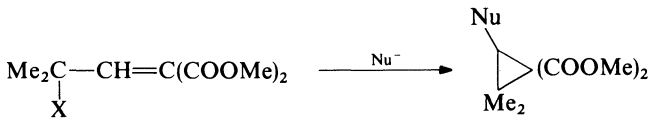
species and are thus susceptible to a direct nucleophilic displacement at the γ-carbon, as well. Indeed, the course of the reaction of methyl γ- bromocrotonate with a thiolate anion is critically dependent upon the nature of the solvent and the thiolate gegen ion[101]. It has also been found[102] that the reaction of γ-bromocrotonate with rather stable ester enolates, such as malonate anion, proceeds preferentially in a direct S_N2 manner,

whereas the reaction with reactive enolates occurs in a 'Michael-initiated ring-closure' (equation 22)[103].



(22)

γ-Branched γ-bromoalkylidenemalonic esters have been found to give three-membered ring products in their reactions with a variety of nucleophiles, such as $NaBH_4$[104], Grignard reagents[105], cyanide, methoxide and thiolate anions (equation 23)[106, 107]. Related reactions are those of γ-bromo-α,β-unsaturated sulfones with Grignard reagents[108] and of 6-oxiranylfulvenes with alkyllithium which give 1-hydroxymethylspiro[2.4]hepta-4,6-dienes[109]. The latter reaction is initiated by the addition of the organolithiums to the C (6) of the fulvene.

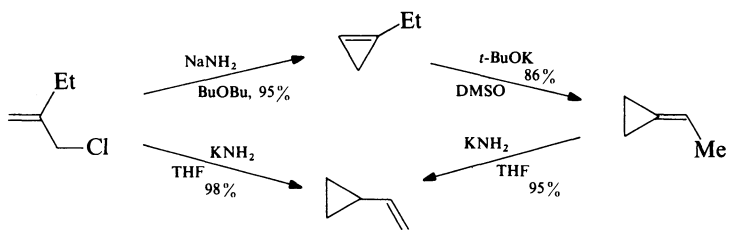


(23)

Nu = OMe, CN, SR, H, $CH{=}CMe_2$

2. *Reactions of other allylic derivatives*

The preparation of cyclopropene has been achieved in the reaction of allyl chloride with sodium amide[110]. 1-Alkylcyclopropenes have analogously been synthesized from 2- and 3-alkylallyl chlorides[111], but the products are liable to isomerize under the strongly basic conditions to alkylidenecyclopropanes and 1-alkenylcyclopropanes. The use of potassium amide gives the rearranged products in a higher extent than that with sodium amide (equation 24)[112]. Methylenecyclopropane has been prepared by the successive treatments

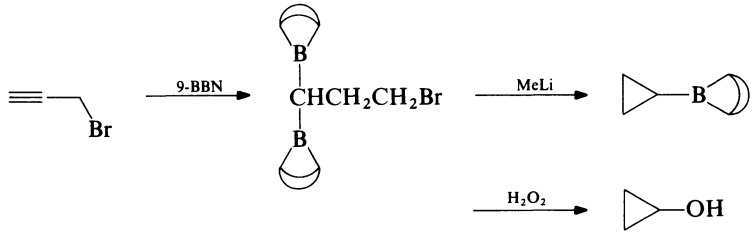


(24)

of 3-chloro-2-methylpropene with sodium amide and *t*-BuOK, exploiting the isomerization of the initially formed 1-methylcyclopropene[113]. The cyclization of allylic chlorides to cyclopropenes can also be effected with alkyl- or phenyllithium[114], but the double bond in the cyclopropene is prone to undergo the addition of organolithium reagents. In fact, the treatment of 1-chloro-2-methylcycloalkenes with excess organolithium reagents results in the formation of their adducts to the double bond of the bicyclic cyclopropene intermediates[115].

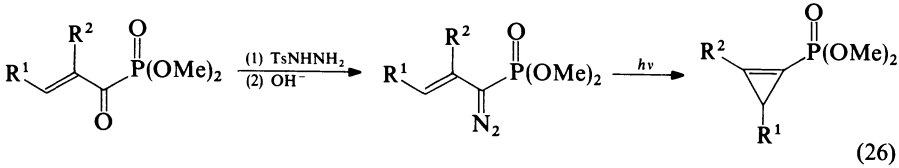
The hydroboration of allylic chlorides provides cyclopropane derivatives when the produced organoboranes are treated with base[116]. The simple hydroboration with

diborane, however, leads to the formation of alkenes in substantial proportions. These are derived from the hydroboration of the allylic halides with undesirable, inverse orientation. The yields of the three-membered ring products have, however, been markedly improved by the use of 9-borabicyclo[3.3.1]nonane (9-BBN)[117]. The treatment of 3-vinylpropanolides with 9-BBN produces cyclopropaneacetic acids[118]. The dihydroboration of 2-propynyl bromide with 9-BBN followed by the MeLi treatment provides *B*-cyclopropyl-9-BBN. The subsequent treatment of this product with hydrogen peroxide gives cyclopropanol (equation 25)[119].



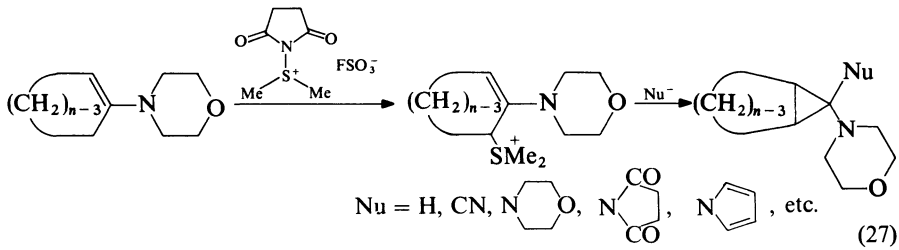
(25)

A variety of cyclopropene derivatives have been prepared by means of thermolysis[120] or photolysis[121] of alkenyldiazomethanes, which are obtainable from α,β-unsaturated aldehydes or ketones via the corresponding tosylhydrazones (equation 26). Cyclic allylic



(26)

chlorides[122] as well as the corresponding sulfonium salts[123–126] which carry an amino group at C(2), react with various nucleophiles to give 1-substituted bicyclic cyclopropylamines, such as cyclopropanone aminals, via the C(1)–C(3) bond formation (equation 27). α-Branched ester enolates add to the central carbon atom of π-allyl palladium complexes to give α-cyclopropyl esters with the ejection of the palladium (equation 28)[127].



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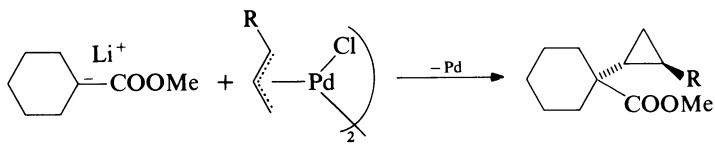
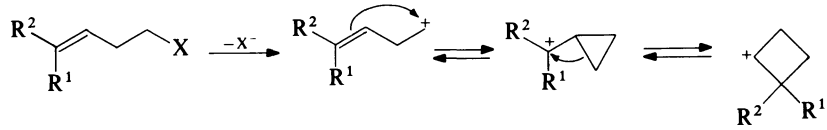


(28)

R = H, Me, COOMe

E. Cyclization of 3-Butenyl Derivatives

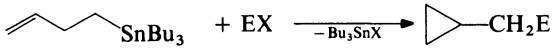
3-Butenyl halides or sulfonates cyclize under solvolytic conditions to give cyclopropylmethyl derivatives (equation 29) when the substituents stabilize the cyclopropylmethyl



(29)

cation relative to the 3-butenyl and the cyclobutyl cations[128–130]. The cyclization of 3-butenyl derivatives to the corresponding cyclopropylmethyl compounds occurs merely under kinetic control, since the latter is generally thermodynamically less stable than the former. Certain 3-butenyl halides and sulfonates undergo simultaneous cyclization–hydrogenolysis upon treatment with LAH[131] or under the conditions of catalytic hydrogenation[132]. Three-membered ring hydrocarbons are obtained in these reactions.

Organometallic compounds with a 3-butenyl moiety can produce cyclopropylmethyl derivatives *via* an addition of electrophiles to the terminal carbon atom of the double bond followed by the loss of the metallic group. 3-Butenylsilanes[133], -stannanes (equation 30)[31,134], -iron[135] and -cobalt[136] are the representative compounds. Thus, the reaction of 3-butenyl trimethylsilane with acyl halides/$TiCl_4$ gives cyclopropylmethyl ketones in satisfactory yields (equation 31)[133]. In an analogous manner, the treatment of 2-(4-pyridyl)ethyl metallic derivatives with acyl halides leads to the formation of *N*-acylated 6-azaspiro[2.5]octadiene derivatives[137].

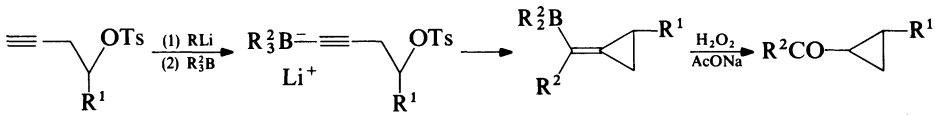


(30)

$EX = Cl_2, Br_2, I_2, HgCl_2, ArSCl, SO_3$

(31)

The successive treatments of 3-butynyl sulfonates with alkyllithium and trialkylborane afford 4-alkyl-4-borylmethylenecyclopropanes, which provide cyclopropyl ketones upon oxidation (equation 32)[138]. The 3-butynyl sulfonates react also with $PhMe_2SiMgMe/CuI$



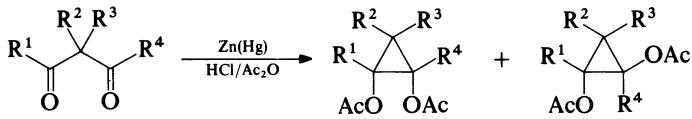
(32)

to give 4-silylmethylenecyclopropanes[139]. Certain Michael acceptors, in which the δ-carbon atom is substituted by an efficient leaving group, produce cyclopropyl derivatives by C_β–C_δ bond formation when treated with lithium dialkylcuprate[140].

F. Bond Formation between Two Unsaturated Groups

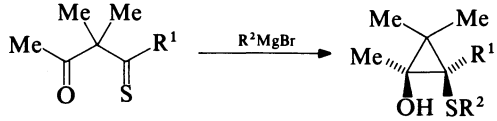
The intramolecular coupling of β-diketones to give 1,2-cyclopropanediols has been effected for non-enolizable 2,2-disubstituted β-diketones with $Zn(Hg)/Ac_2O/HCl$[141],

Li/liq NH_3[142], or by electrolysis[143]. Enolizable β-diketones give the three-membered rings only when they are mainly in the diketo form (R^2 and /or R^3 = H in equation 33)[141]. Analogous reactions of vinylogues affording 2-(acylmethyl)cyclopropanols are also known[144].



(33)

Dimethylmalonic esters give bistrimethylsilyl ether of 3,3-dimethylcyclopropane-1,2-diol upon treatment with Na/Me_3SiCl in liquid ammonia[145]. The McMurry coupling of β-diketones to produce cyclopropenes has so far been limited to aromatic diketones. Thus, 3,3-dialkyl-1,2-diphenylcyclopropenes have been prepared from the corresponding dibenzoylmethanes[146]. Non-enolizable 3-oxothiones[147] and a substituted 1,3-cyclobutanedithione[148] have been found to give 2-(alkylthio)cyclopropanols and 1,3-bis(alkylthio)bicyclo[1.1.0]butanes, respectively, in the reactions with Grignard reagents

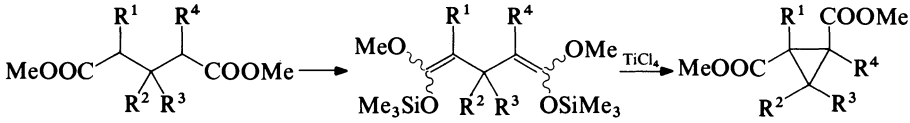


(34)

R^1 = Me, SMe

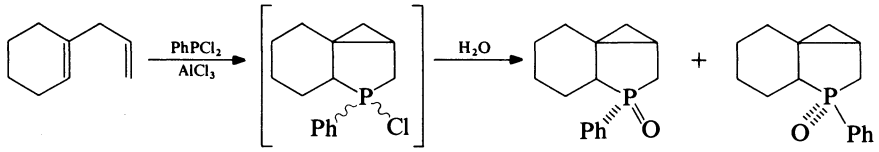
(equation 34). The configuration of the products has been assigned as *cis*. The reactions proceed via thiophilic addition of the Grignard reagent followed by cyclization.

Treatment of bistrimethylsilyl enol ethers of glutaric esters with $TiCl_4$ leads to the stereoselective formation of *trans*-1,2-cyclopropanedicarboxylic esters (equation 35)[149].



(35)

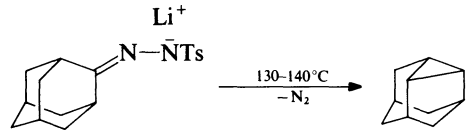
Oxidation of polyalkyl-substituted 1,2,5-hexatrienes with *m*-chloroperbenzoic acid produces bicyclo[3.1.0]hexan-2-one derivatives[150]. Certain 1,4-dienes undergo homoconjugative addition of phosphorus reagents to give 3-phosphabicyclo[3.1.0]hexane derivatives (equation 36)[151].



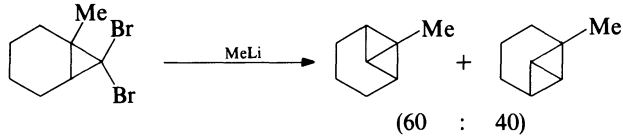
(36)

G. Miscellaneous

Alkyl- and dialkylcarbenes can react with α- or β-C–H groups, giving an intramolecular insertion. The insertion into the α-C–H bond will produce olefins whereas the reaction with the β-C–H group will produce cyclopropanes[152, 153]. The cyclopropane formation becomes more important with the increased branching in the alkyl groups at the α-carbon atom. The coplanar arrangement of the divalent carbon, the α-carbon, and the β-C–H bond favors the formation of the three-membered ring. Inhibition of the olefin formation by the Bredt's rule strongly favors the production of the cyclopropane derivatives as shown in equation 37[154]. Cyclopropylidenes bearing alkyl groups can collapse in two ways; namely, by bicyclo[1.1.0]butane formation by insertion and by rearrangement to allenes. The reactions of tetraalkyl-substituted gem-dibromocyclopropanes[155] and 7,7-dibromobicyclo[4.1.0]heptanes[156] with alkyllithium predominantly produce the insertion products (e.g., equation 38).

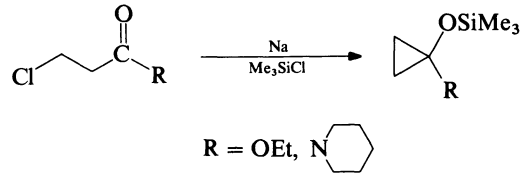


(37)



(38)

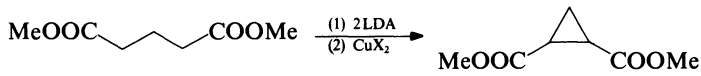
Treatment of 3-chloropropionic esters with sodium in the presence of chlorotrimethylsilane provides a convenient route to cyclopropanone hemiacetals[157]. The corresponding



(39)

amides give 1-silyloxycyclopropylamines (equation 39)[158]. The lithiation of β-bromoketones[159] or -aldehydes[160] lacking an acidic α-hydrogen produces intramolecularly cyclized cyclopropanols.

Dilithium enolates of glutaric esters undergo oxidative coupling to produce 1,2-cyclopropanedicarboxylic esters[161, 162]. Cupric halides have been found to be the most satisfactory reagents for this coupling among various oxidants examined (equation 40)[162].

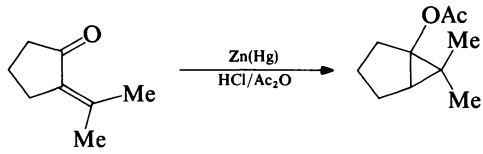


(40)

cis/*trans* = 1.0–3.8

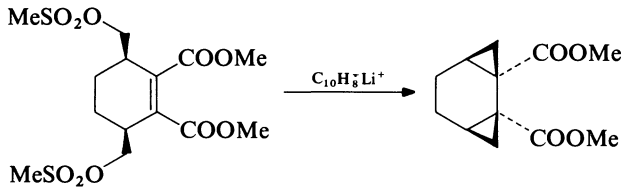
The Clemmensen reduction of α,β-unsaturated ketones under anhydrous conditions ($Zn(Hg)/Ac_2O/HCl$ in ether) affords cyclopropanol acetates via a reductive C(1)–C(3)

bond formation (equation 41)[163]. Treatment of cinnamic ester derivatives with LAH in refluxing THF or dimethoxyethane produces three-membered ring hydrocarbons[164].



(41)

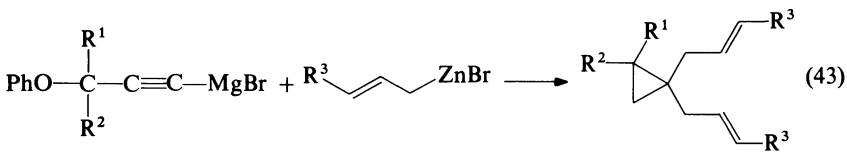
Certain suitably substituted maleic esters, such as **1**, give dicyclopropyl derivatives, **2**, by the successive two-electron transfer from naphthalenide anion radicals and intramolecular



(42)

(1) **(2)**

displacement reactions (equation 42)[165]. The reaction of methoxyallene with trialkylboranes provides 1-alkyl-1-methoxycyclopropanes[166]. Irradiation of 3-morpholinopropiophenones with UV light produces 2-morpholino-1-phenylcyclopropanols in good yields[167]. 1,1-Diallylcyclopropanes and related compounds have been obtained in the reaction of 2-propynyl derivatives with allylzinc halides (equation 43)[168].



(43)

III. COMBINATION OF C_2 AND C_1 BUILDING BLOCKS

A. Cyclopropanation of Carbon–Carbon Multiple Bonds with Carbenes and Carbenoids

Carbene reactions have been a subject of numerous reviews in recent years. In addition to a comprehensive review by Kirmse[152], the generation of carbenes and carbenoids from various precursors has also been summarized[35, 153, 169]. Moreover, the novel advancement in the chemistry of carbenes has been surveyed in a serial publication[170]. Other numerous review articles on particular carbenes are cited in the relevant subsections. It should be noted that not in all the reactions described in this section was it experimentally confirmed that the reactions proceed via carbenes or carbenoids. Some thermal cyclopropanation reactions with diazo compounds might proceed via 1-pyrazolines which simply evaded detection. Reactions in which the pyrazoline is detected or isolated are described separately in Section II.B. Formation of cyclopropanes via a radical or an ionic intermediate may also be included in this section.

The relative reactivity of alkenes toward various carbenes and carbenoids has been compiled[171]. Recently, a selectivity index, m_{CXY}, which can be estimated from the dual

parameter equation (equation 44), has been proposed as a measure of the olefinic selectivity of carbenes[172]. This index has led to the discovery of ambiphilic carbenes.

$$m_{CXY} = -1.10 \sum_{X,Y} \sigma_R^+ + 0.55 \sum_{X,Y} \sigma_I - 0.31 \quad (44)$$

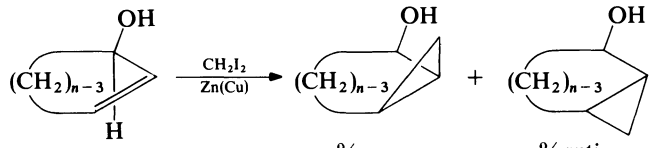
In the following sections, the classification of carbenes bearing two different substituents is made by giving priority to the functional group which will appear in the later subsection. For example, the reaction of :C(Cl)COOEt is described in Section III.A.5 rather than in III.A.4.

1. Methylene

Cyclopropanation of carbon–carbon double bonds with methylene can be achieved in several ways. Aside from the carbene or carbenoid additions, activated multiple bonds may be cyclopropanated by reaction with ylides or by a synthetic route via 1-pyrazolines (see Sections III. B and III. D in this chapter, and also Chapter 9). Addition of halocarbenes followed by hydrogenolysis provides a further route for the cyclopropanes (Section V.A).

The organic reagents prepared from diiodomethane and zinc–copper couple (Zn/Cu) or diiodomethane and diethylzinc have proved to be highly versatile for the cyclopropanation of alkenes (the Simmons–Smith reaction)[173]. The transfer of methylene usually occurs stereospecifically. Moreover, the reaction is free from side reactions, such as olefin isomerization and insertion of the carbenoid intermediate into C–H bonds, which are frequently encountered in the cyclopropane synthesis via carbene additions. The zinc reagents are weakly electrophilic, and hence the cyclopropanation is accelerated by electron-donating substituents at the double bond and retarded by electron-withdrawing groups[174]. Many types of functional groups do not interfere with the reaction. Thus, unsaturated alcohols, amines, ketones and esters, as well as enol ethers and enamines, have successfully been cyclopropanated by the Simmons–Smith procedure. Allenes undergo stepwise cyclopropanations[175], but the reaction of alkynes to give cyclopropenes has so far met with difficulty[176].

The stereochemistry of cyclopropanation by the Simmons–Smith reaction generally follows the principle of steric approach control. The zinc reagents show a propensity to coordinate with oxygen[177] as well as with nitrogen[178] functional groups. Thus, when these heteroatom-carrying substituents are appropriately positioned in the substrate, the methylene transfer is accelerated and directed by them. Generally, the hydroxyl group is more effective in assisting the cyclopropanation and controlling the stereochemistry than ether and ester functions. The reaction occurs at the more accessible face of the double bond with respect to the functional group. This is shown by the *syn/anti* product ratios as a function of ring size (equation 45)[177]. These accelerating and directing effects diminish



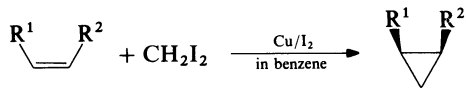
(45)

n	%*syn*	%*anti*
5	> 99	
6	> 99	
7	90	10
8	0.5	99.5
9	0.05	99.95

largely, however, when the coordinating heteroatom is separated from the double bond by three carbons or more. Carbonyl groups in certain α,β-unsaturated ketones also exhibit some activating effect to the reaction of the zinc reagents[179]. In this case, however, the effect is very much dependent on the structure of the ketone. It has been suggested that easily enolizable ketones tend to give poor results.

With regard to the preparation of the Zn/Cu couple, several methods have been developed[180, 181]. Dibromomethane may be used instead of diiodomethane when a specifically prepared Zn/Cu couple is applied[181, 182]. The use of Zn/Ag couple often gives better results[183]. Ultrasound irradiation of the reaction mixture has been shown to facilitate the reaction[184]. The cyclopropanation of alkenes with diiodomethane and diethylzinc can be carried out in hydrocarbon solvents and is particularly suitable with easily polymerizable olefins such as vinyl ethers[185]. It has been reported that molecular oxygen remarkably promotes the reaction of diiodomethane with diethylzinc and substantially increases the yield of the adducts[186]. A convenient modification which avoids the handling of pyrophoric diethylzinc has been reported[187]. In reaction of olefins which are sensitive to the unavoidably produced zinc iodide (the Lewis acid), the addition of one equivalent of dimethoxyethane (DME) to the solvent has been recommended[188]. Zinc iodide is then precipitated as the 1 : 1 DME complex as it is formed. Zinc salts, which often complicate the workup of the reaction mixture, can also be removed as precipitates by the addition of pyridine prior to the workup[183].

An organocopper reagent capable of transferring methylene to olefinic double bonds has been generated from diiodomethane and copper powder in aromatic hydrocarbon solvents (equation 46)[189]. The reactivity of this reagent toward alkenes is similar to that of

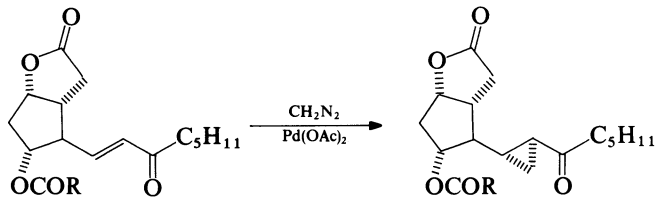


(46)

the zinc reagents: it gives cyclopropanation of electron-rich double bonds in preference to electron-deficient ones, and the reaction is stereochemically controlled by appropriately positioned oxygen functions. In contrast, the reagent prepared from dibromomethane and a Ni (0) complex reacts merely with electron-deficient olefins[190]. Thus, the nickel reagent is complementary to the organozinc and organocopper reagents so far as the chemical selectivity is concerned. Diiodomethane transfers the methylene group to olefinic double bonds upon irradiation of the mixture of the two components with a sunlamp[191].The reactions have been found to be stereospecific in most cases, and are less sensitive to steric hindrance compared with the Simmons–Smith reaction.

Methylene ($:CH_2$) generated photochemically or thermally from diazomethane is highly reactive and is prone to incur side reactions to a substantial extent. In order to avoid these undesirable complexities, the cyclopropanation of multiple bonds with diazomethane has usually been carried out under catalytic conditions[33–37, 192]. The catalysts most frequently employed are copper salts and copper complexes as well as palladium acetate. The intermediate produced in the copper salt-catalyzed reactions behaves as a weak electrophile and exhibits a preference to attack an electron-rich double bond. It is also reactive enough to attack aromatic nuclei. In contrast, the palladium acetate-catalyzed decomposition of diazomethane cyclopropanates α,α- or α,β-disubstituted α,β-unsaturated carbonyl compounds in high yields (equation 47)[193]. The trisubstituted derivatives, however, do not react. The palladium acetate-catalyzed reaction has been applied also for the cyclopropanations of some strained cyclic alkenes[194], styrene derivatives[51, 195] and terminal double bonds[196]. However, the cyclopropanation of non-activated, internal double bonds occurs only with difficulty. The difference, thereby,

permits the selective cyclopropanation of the former types of double bonds in the presence of the latter (equation 48)[196].



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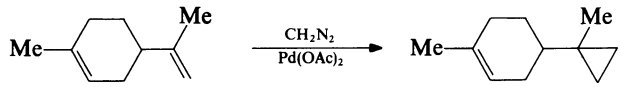
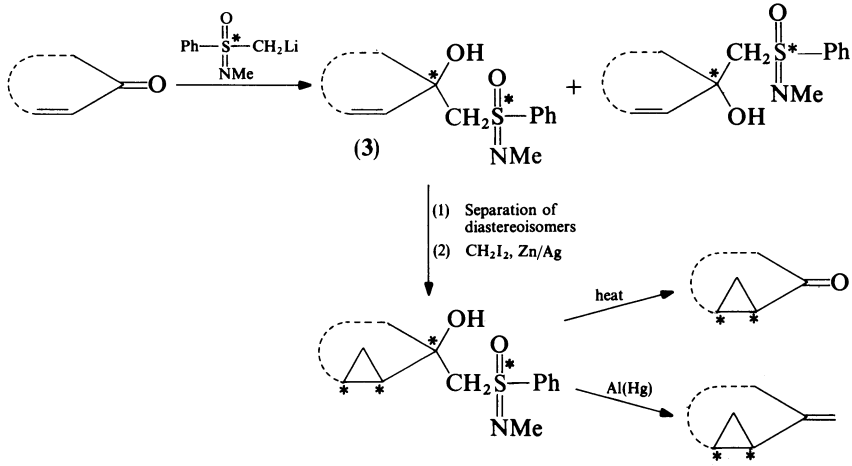


(48)

Satisfactory asymmetric cyclopropanations of olefins bearing chiral substituents have been achieved in several cases[51, 197, 198]. A variety of cyclopropyl ketones as well as vinylcyclopropanes have been prepared in optically pure forms from α,β-unsaturated ketones via chiral sulfoximine adducts, **3** (equation 49)[199].



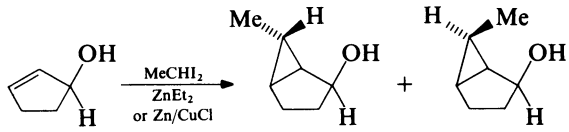
(49)

Other reagents capable of transferring methylene include CH_2N_2/ZnI_2, $CH_2N_2/PhCH_2HgI$[200], $Ph_2\overset{+}{S}\text{-}\overline{C}H_2/Cu(acac)_2$[201], $(C_5H_5)(CO)_2Fe(CH_2\overset{+}{S}Me_2)\ I\cdot BF_4^-$[202] and $CH_2BrCl/BuLi$[203].

2. *Alkyl-, alkenyl- and arylcarbenes*

Since alkyl- and dialkylcarbenes undergo rapid intramolecular insertion into α- and β-C–H bonds, the intermolecular addition of these species to olefinic double bonds is not practical (Sections II.B, II.G)[152]. Merely, the intramolecular reactions produce three-membered ring products in acceptable yields.

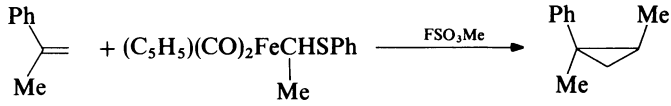
The application of carbenoid reactions, however, gives satisfactory results in certain cases. Thus, ethylidene iodide with diethylzinc transfers an ethylidene group to olefinic double bonds in good yields[204]. The reaction proceeds in a stereospecific manner (equation 50). Stereochemical control of the addition by hydroxyl groups similar to those



(50)

(76 : 24)

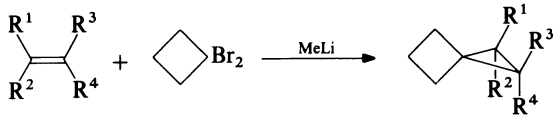
described for the Simmons–Smith reaction (Section III.A.1) has also been noted in this reaction. For the cyclopropanation of allylic alcohols, Zn dust/CuCl can be used in place of $ZnEt_2$[205]. The iron complex, $(C_5H_5)(CO)_2FeCHMeSPh$, upon treatment with methyl fluorosulfate in the presence of alkenes, affords methylcyclopropanes (equation 51)[206].



(51)

(Z/E = 41/17)

trans-Alkenes, however, have failed to react. With $(C_5H_5)(CO)(PPh_2R^*)Fe=CHMe$ bearing a chiral phosphine ligand, an asymmetric cyclopropanation of styrene has been accomplished[207]. Treatment of 2,2-dibromopropane[208,209] and 1,1-dibromocyclobutane[210] with MeLi in the presence of alkenes gives gem-dimethylcyclopropanes and spiro[2.3]hexane derivatives (equation 52), respectively. These reactions proceed stereospecifically. The iron complex, $(C_5H_5)(CO)_2\overset{+}{F}e=CMe_2\cdot BF_4^-$, has been found to transfer a



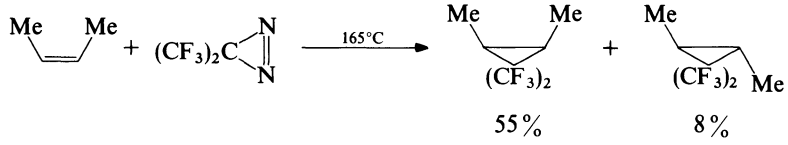
(52)

2-propylidene group to olefins[211]. Cyclopropylidenes derived from *N*-nitrosomethylureas[212] or from gem-dibromocyclopropanes[213] have been added to olefinic double bonds to give spiropentanes. The isomerization of the intermediate to allenes may compete with the cyclopropanation. Highly strained bicyclobutane derivatives have been prepared by the intramolecular cyclization of 3-butenylidenes, which are thermally generated from the sodium salts of the corresponding 3-butenone tosylhydrazones (equation 53)[214]. In contrast to normal alkylcarbenes, the intermolecular additions

(53)

have successfully been executed with trifluoromethylcarbenes. Thus, trifluoromethylcarbene photochemically generated from the diazo precursor adds to alkenes as well as alkynes[215]. Thermolysis of bis(trifluoromethyl)diazomethane or -diazirine produces

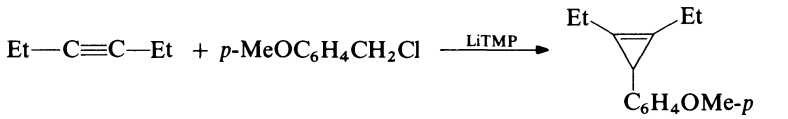
bis(trifluoromethyl)carbene, which has been trapped by alkenes with partial loss of stereochemical integrity of the starting olefin (equation 54)[216]. gem-Bis(trifluoromethyl)cyclopropanes have also been obtained in the thermal reaction of hexafluoroacetone azine with alkenes[217].



(54)

A 2-propenylidene transfer reaction utilizing vinyldiazomethane has been examined under copper-catalyzed conditions. $Cu(OTf)_2$ and $Cu(acac\text{-}F_6)_2$ have been found to be the catalysts of choice[218]. Dichloropropenes transfer 2-propenylidenes to electron-deficient double bonds upon treatment with a copper–isocyanide complex[219].

Arylchloromethanes with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) (e.g. equation 55)[220], aromatic aldehydes with Zn/BF_3 (equation 56)[221], zinc halide-catalyzed decomposition of aryldiazomethanes[222], benzal halides with alkyllithium[223, 224]



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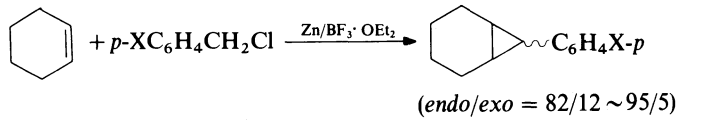


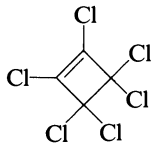
(56)

X = H, Me, OMe, Cl

and benzal iodide with $ZnEt_2$[225] all satisfactorily transfer arylmethylenes to carbon–carbon multiple bonds. These carbenoid reactions proceed in a stereospecific manner and produce predominantly the thermodynamically less stable *syn*-adducts. The transition metal carbene complexes, $(CO)_5W{=}CHPh$[226] and $(C_5H_5)(CO)Fe{=}CHPh^+ \cdot PF_6^-$[227] also react with alkenes to give phenylcyclopropanes stereospecifically. The latter reagent exhibits a remarkably high *syn*-selectivity. These reactions are not carbenic, but the intermediacy of metallacyclobutanes has been proposed. Arylmethylenes have also been generated by the photolysis of aryldiazomethanes[223, 228] or of stilbene oxides[229]. The addition reactions to alkenes are largely stereospecific, but the *syn/anti*-selectivity cannot be expected.

The reactions of diphenylmethylene and fluorenylidene with olefinic double bonds are not stereospecific. Photochemical or thermal decomposition of diphenyldiazomethane in the presence of alkenes is often accompanied by the formation of a substantial amount of non-cyclic products derived from abstraction–recombination reactions[230]. The extent of hydrogen abstraction relative to addition is highly dependent on the substitution pattern of the olefin[231]. In contrast, fluorenylidene generated from 9-diazofluorene usually gives cyclopropanes as the major product[232]. Cyclopentadienylidene and its substituted analogues can be generated from the corresponding diazo precursors. They react with olefinic as well as with acetylenic substrates[35, 233]. Cycloheptatrienylidene preferentially

adds to electron-deficient double bonds[234]. Other alkylidene transfer reactions including **4** with alkyllithium[235], photolysis of **5**[236] and thermolysis of **6**[237] have been reported.



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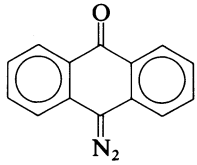

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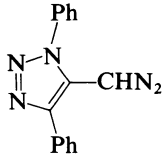
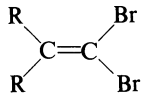


(6)

3. *Alkenylidenes*

Vinylidenes have been transferred from a variety of precursors to olefins to produce methylenecyclopropanes[238]. Because of ready intramolecular hydrogen shifts to give terminal acetylenes, the addition of vinylidene to olefins is rather limited to 2,2-disubstituted species. The methodologies so far developed include: (1) gem-dibromides, **7**, with MeLi[239], (2) vinyl halides[240] or vinyl triflates, **8**[241] with *t*-BuOK, (3) the fluoride ion promoted decomposition of vinylsilanes, **9**[242,243], (4) thermolysis of mercuric derivatives, **10**, at 250 °C[244], (5) decomposition of vinylazo compounds, **11**, at 25 °C[243], (6) the alkaline decomposition of *N*-nitroso-oxazolidones, **12**[245], (7) the basic decomposition of *N*-nitrosoacetamides, **13**[246] and (8) ketones with diazomethylphosphonates (equation 57)[247].



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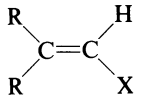
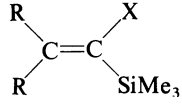


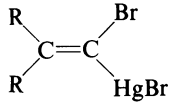
(X = Cl, Br, OTf)

(8)



(X = Cl, OTf)

(9)



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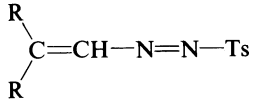

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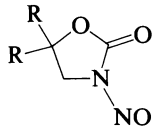

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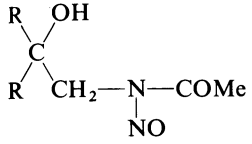
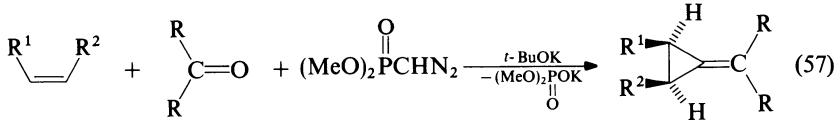


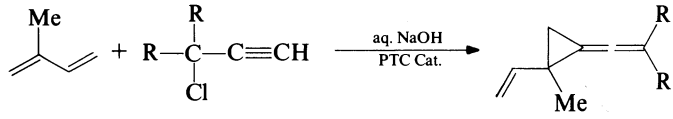
(13)



(57)

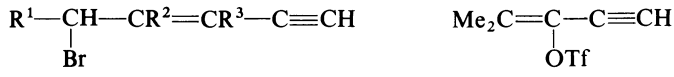
The reactions of **9**, **10** and **11** can be carried out under neutral conditions. The decomposition of **13** under phase transfer catalyzed (PTC) conditions usually gives the adducts in yields better than those obtained in the alkoxide-induced decomposition of **12**. The reactions of 2,2-disubstituted vinylidenes are rather sensitive to steric hindrance. The stereospecificity of the addition has been demonstrated in the reaction of **12**. Intramolecular reactions giving particularly strained methylenecyclopropanes have also been reported[248].

3,3-Dialkyl-1,2-propadienylidenes have been transferred readily from 1,1-dialkyl-2-propynyl chlorides (equation 58)[249] or 3,3-dialkyl-1,2-propadienyl bromides[250] to olefins under the PTC conditions. The yields of the adducts are usually better than those obtained



(58)

by using *t*-BuOK[251]. 3,3-Dichloro-1,2-propadienylidene adducts have been obtained in the reactions of alkenes with 1,1,3,3- or 1,2,3,3-tetrachloropropene in the presence of *t*-BuOK[252]. The treatment of enyne derivatives, **14** and **15**, with *t*-BuOK effects the



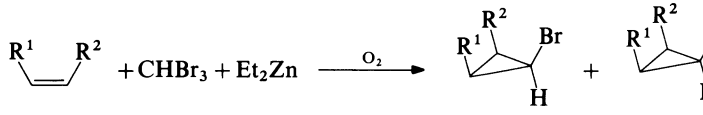
(14) **(15)**

transfer of 3-alkenyl-1,2-propadienylidenes[253] and 4,4-dimethyl-1,2,3-butatrienylidene[254] to olefinic double bonds, respectively.

4. Monohalo- and dihalocarbenes[255]

The addition of monohalo- and dihalocarbenes or carbenoids to alkenes occurs stereospecifically with few exceptions[256]. These species behave as electrophiles and the reactivity of simple alkenes toward dihalocarbenes falls off in the following order: tetra- > tri- > *unsym*-di- > *sym*-di- > monoalkyl-substituted olefins. The additions of monohalocarbenes generated by α-elimination usually produce *syn*-adducts preferentially, but the degree of *syn*-stereoselectivity appears to be less prominent in the addition of carbenes carrying heavy halogens. In contrast, halocarbenes generated by thermolysis of halodiazomethanes show little *syn*/*anti*-selectivity[257]. The dihalocarbene adducts of strained alkenes including cyclopentene and norbornene derivatives, are liable to undergo rearrangements, often defying the isolation of the three-membered ring products[258–260].

The treatment of alkenes with trihalomethane and $ZnEt_2$ affords monohalocyclopropanes in good yields[261,262]. Molecular oxygen markedly accelerates the reaction (equation 59)[262]. Dichloromethane with MeLi or LDA[263] as well as chlorodiiodomethane

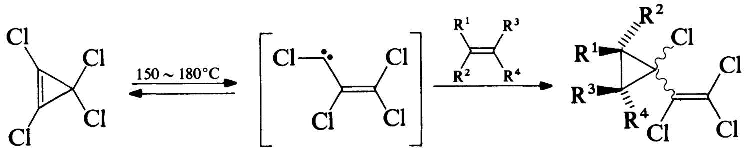


(59)

% *syn*-Br > % *anti*-Br

with copper powder[189] transfers chloromethylene to unsaturated carbon–carbon bonds. In this reaction, MeLi should be prepared from methyl chloride and lithium, since the reagent prepared from methyl bromide or methyl iodide often complicates the reaction owing to undesirable side reactions[264]. Bromocyclopropanes are obtained in the reaction of $CH_2Br_2/(Me_3Si)_2NLi$[265] or $CHBr_3/RLi$[266] with alkenes. Thermolysis of phenyl (dihalomethyl) mercuries[267] or halodiazomethanes[257] as well as photolysis of halodiiodomethanes[268] in the presence of alkenes provides monohalocyclopropanes under neutral reaction conditions.

Alkylchlorocarbenes, generated photochemically from the corresponding diazirines, add to alkenes in fair to good yields[269]. The reactions are stereospecific as well as stereoselective, although the isomeric cyclopropanes produced have not been configurationally characterized. $F_3SiCF_2CHF_2$[270], $PhHgCFBrCF_3$[271] and $PhHgCClBrCF_3$[272] transfer $:CFCHF_2$, $:CFCF_3$ and $:CClCF_3$, respectively, upon thermolysis at 140–150°C in neat alkenes. The reactions are stereospecific. Polychlorocyclopropanes undergo reversible thermal ring cleavage to give polychloro-2-propenylidenes, which have successfully been trapped by alkenes in good yields (equation 60)[273]. Polyhalo-2-propenylidenes[274] including 1-chloro-2-propenylidene[275] have also been generated from

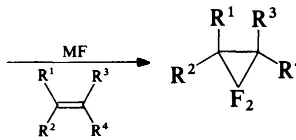


(60)

halogenated propenes by α-elimination and added to a variety of olefins in moderate yields. 1-Halobenzylidenes have been produced either by α-elimination of benzal halides[276,277] or by photolysis or thermolysis of the corresponding diazirines[277,278]. Their additions to alkenes preferentially give the isomers in which the halogen is located *syn* to the more congested side of the three-membered ring.

Difluorocarbene has been generated from $CF_2ClCOONa$[279], Me_3SnCF_3 with or without NaI[280], $PhHgCF_3$ with NaI[281], CHF_2Cl/oxirane/$Bu_4N^+Cl^-$[282], CF_2Br_2/PPh_3 with CsF or KF (equation 61)[283], difluorodiazirine[284], $(CF_3)_3PF_2$[285] and

$$CF_2Br_2 + R_3P \longrightarrow [R_3PCF_2Br]^+Br^-$$

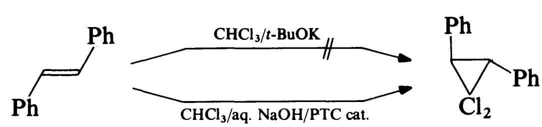


$+ R_3PFBr + MF$ (61)

$M = Cs, K;\quad R = Ph, Me_2N$

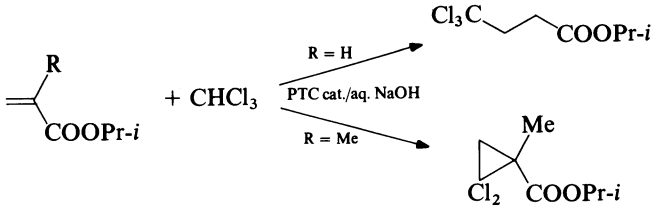
1,2-epoxyperfluoropropane[286]. The Me_3SnCF_3/NaI and $PhHgCF_3$/NaI systems transfer $:CF_2$ to a wide variety of olefiins in good yields. $CF_2ClCOONa$ has been used in the reaction of steroids. The CF_2Br_2/PPh_3 method gives excellent results with tri- and tetrasubstituted alkenes. The thermolysis of Me_3SnCF_3, $(CF_3)_3PF_2$, or 1,2-epoxyperfluoropropane has been utilized in the cyclopropanation of polyhalogenated alkenes and alkynes.

The cyclopropanation of alkenes with dihalocarbenes, $:CX_2$ or $:CX^1X^2$, except for $:CF_2$, can be efficiently executed by the PTC procedures (CHX_3/strong aqueous base/catalyst), which are well-documented in books[258–260] and reviews[287]. The dichloro- and dibromocarbene additions by the PTC procedure have successfully been applied for many alkenes, conjugated polyolefins and allenes. Satisfactory results are also reported for the reactions of sterically hindered olefins as well as electronically deactivated olefins, which frequently



(62)

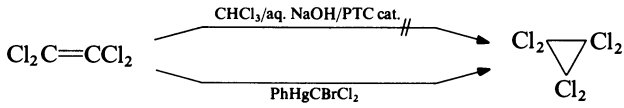
resist the dihalocarbene addition carried out by standard procedures (equation 62)[258-260]. Recently, further modifications, such as $CCl_3COONa/CHCl_3$/catalyst[288], powdered $NaOH/CHCl_3$/catalyst[289] and powdered $NaOH/CHCl_3$/ultrasonic irradiation[290] have also been developed. α,β-Unsaturated ketones, esters, nitriles, and sulfones give, however, the Michael adducts of the trihalomethyl anion, unless the α-position is substituted by an alkyl group (equation 63)[291]. In the reactions of polyunsaturated



(63)

compounds, dihalocarbene generally adds first to the more highly substituted double bond selectively. However, multiple additions are also common under PTC conditions. The catalysts and reaction conditions to afford monoaddition products have been investigated[292].

The Seyferth's reagents ($PhHgCX_3$) are particularly effective for the cyclopropanation of deactivated or base-sensitive substrates, such as allyl halides, allyl isocyanates, and polychloroalkenes (e.g. equation 64) as well as α,β-unsaturated ketones, esters, nitriles, and sulfones[293]. The Michael addition of a trihalomethyl unit has not been observed in this



(64)

type of cyclopropanation. Sodium trichloroacetate also shows an excellent $:CCl_2$ transfer reactivity comparable or somewhat superior to the PTC procedures[294]. Trifluoro(trichloromethyl)silane transfers dichloromethylene to highly electron-deficient alkenes and alkynes in vapor phase thermolysis[295]. The addition of dichlorocarbene to alkynes and subsequent hydrolysis during the aqueous workup affords cyclopropenones[208,296].

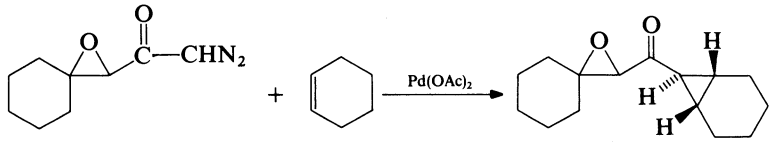
Since dibromocarbene is more susceptible to hydrolysis than dichlorocarbene, dibromocarbene addition by the PTC method often gives the expected adducts in lower yields than those of the dichlorocarbene addition. Use of excess tribromomethane[297], execution of the reaction at ambient or lower temperature[297] and addition of a small amount of alcohol[298] have been recommended to improve the yields. Diiodocarbene has also been generated by PTC procedures and has been added to alkenes[299]. However, the CHI_3/*t*-BuOK method appears to be superior[300]. It has also been pointed out that the $:CI_2$ adducts are sometimes rather unstable when they are prepared by the PTC method, probably due to contamination of some sensitive byproducts[260].

Dihalocarbenes carrying two different halogenes, namely, :CFCl[301,302], :CFBr[302,303], :CFI[304], :CClBr[293,305] and :CClI[299] have also been generated by various methods including PTC procedures. In the reactions of :CFCl and :CFBr, it has been found that the sterically more congested isomer has usually predominated, i.e., the fluorine is frequently placed *anti* to the larger number of alkyl substituents.

5. *Acyl- and alkoxycarbonylcarbenes*

Acyl- and alkoxycarbonylcarbenes are usually generated from the corresponding diazo compounds[35,306]. The thermal or photochemical reactions of acyl and alkoxycarbonyl diazo compounds in the presence of olefinic substrates are, however, frequently accompanied by C–H insertion reactions, hydrogen abstractions, 1,3-dipolar additions (Section III.D), and Wolff rearrangement. In order to avoid complication due to these side reactions, catalytic decomposition of diazo precursors is generally employed. The most frequently used catalysts are copper powder and copper salts. Since they are practically insoluble in organic solvents, the decomposition occurs in the manner of heterogeneous catalysis. Recently, however, soluble complexes of rhodium, palladium, and copper have been exploited and used with increasing frequency to carry out the homogeneous catalytic decomposition of the diazo compounds. In general, acyl- and alkoxycarbonyldiazomethanes react with alkenes stereospecifically under the catalytic conditions. The addition of divalent species usually occurs preferentially to the less hindered side of the double bond. In the reactions of these carbonylcarbenes, the sterically less congested *anti*-isomers are usually predominantly produced. Asymmetric cyclopropanation with a high degree of enantiomeric excess has also been realized with the chiral, homogeneous catalysts.

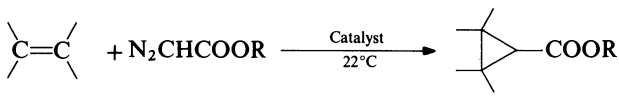
A variety of acylcyclopropanes, including acetyl-[307] and benzoylcyclopropanes[308] as well as their substituted analogues (e.g. equation 65)[309], have been prepared by these procedures. The copper-catalyzed transfer of benzoylmethylene to *cis*-2-butene is not



(65)

completely stereospecific. The photochemical reaction results in production of cyclopropyl compounds in much lower yields than the metal-catalyzed reactions, and proceeds usually with an extensive loss of olefin stereochemistry. In the presence of molybdenum complexes, the reactive species generated from benzoyl- and alkoxycarbonyldiazomethanes exhibit nucleophilic properties and thus add merely to electron-demanding alkenes[310]. The same diazomethanes can react with α,β-unsaturated carbonyl compounds in the presence of SbF_5 to give cyclopropyl derivatives[311].

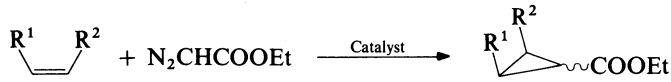
The reaction of diazoacetic esters with alkenes is stereospecific and *anti*-isomers are produced preferentially. However, the *anti*/*syn* ratio is markedly dependent on the catalyst utilized. In order to prepare the three-membered adducts in better yields, with higher stereoselectivity, or with higher optical yields, extensive investigations have been conducted. Among the various catalysts examined, rhodium carboxylates have been found to be very efficient (equation 66)[312, 313]. The reaction is relatively insensitive to steric



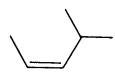
(66)

	Yields of the adduct (%)[312]		
	$Pd(OAc)_2$	$Cu(OTf)_2$	$Rh_2(OAc)_4$
1-hexene	30	36	86
cyclohexene	21	54	88
styrene	98	80	90

hindrance, and hence is recommended for the cyclopropanation of disubstituted double bonds. $Rh_6(CO)_{16}$ has also been found to be a quite efficient catalyst[314]. Rhodium(III) tetra-arylporphines catalyze the transfer of ethoxycarbonylmethylene to alkenes with relatively high *syn*-selectivity (equation 67)[315]. In contrast, palladium acetate-catalyzed reaction is sensitive to steric hindrance, and is only satisfactorily employed in the cyclopropanation of monosubstituted as well as conjugated or strained cyclic double bonds[316]. The particular advantage of palladium acetate catalysis is, however, its

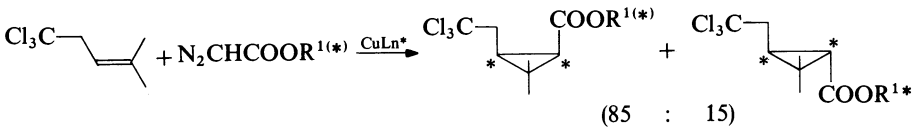


(67)

	syn/anti ratio		
	CuCl	$Rh_2(OCOBu\text{-}t)_4$	Rh(porph)*
	0.12	0.32	1.17
	0.56	2.2	6.52

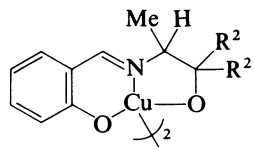
*porph = tetramesitylporphine

compatibility with the presence of electron-withdrawing substituents, such as acetyl or alkoxycarbonyl[193, 316]. Copper catalysts are intermediate in efficiency compared to rhodium and palladium catalysts[312]. The regioselective cyclopropanation of polyenes[317] and allenes[318] have also been developed. Chiral cobalt[319] and copper complexes[320], which give adducts with a high enantioselectivity (up to 95%), have been reported (equation 68). Internal[321] as well as terminal[322] alkynes have been catalytically cyclopropanated to give



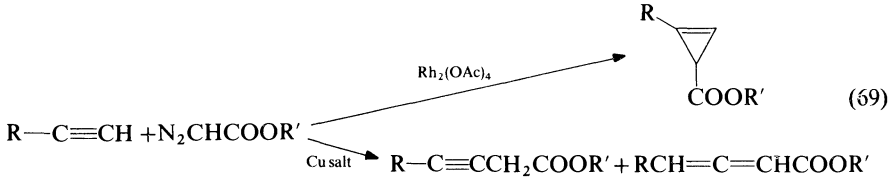
(68)

$R^{1(*)}$	e.e. (%)	
1-menthyl	93	19
ethyl	91	11

CuLn* = 

R^2 = 2-octyloxy-5-*t*-butylphenyl

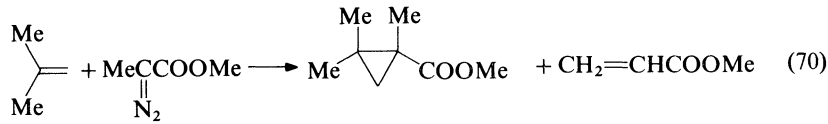
cyclopropenes in good yields (equation 69). The most common side reaction in these reactions is the formation of maleic and fumaric esters from the dimerization of the carbenes. By controlling the rate of addition of diazoacetic esters to the reaction medium,



(69)

however, this competitive dimerization can be minimized and good yields of cyclopropanes are realized even when merely an equimolar mixture of olefin and diazo ester is allowed to react[313].

Alkoxycarbonylmethylenes have also been transferred from dibromoacetic ester with copper[189] as well as from haloacetic esters with Cu_2O/RNC[169b, 323]. In the reactions of terminal alkenes, the former reagents give *syn*-adducts preferentially. The triplet sensitized decomposition of 2-diazopropionic ester in alkenes gives 1-methylcyclopropanecarboxylic esters (equation 70)[324]. In contrast, the direct photolysis of the same diazo ester produces

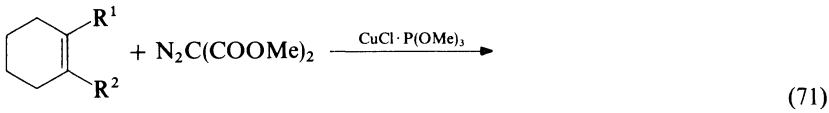


(70)

$h\nu/Ph_2C{=}O$	72%	3%
direct $h\nu$	4%	14%

mainly the acrylic ester. Photolysis of halodiazoacetic esters[325] or thermolysis of PhHgCXYCOOR (X=Y=halogen)[326] transfers alkoxycarbonyl(1-halo)methylenes to alkenes in a stereospecific manner.

Bisalkoxycarbonylcarbenes have been generated from several different sources[327]. In the photochemical reaction of diazomalonic esters, the adducts to alkenes have been obtained with substantial retention of stereochemistry when the singlet species is allowed to react. On the other hand, an almost complete loss of olefin stereochemistry is observed in the reaction of triplet species[328]. Under the catalytic conditions, the cyclopropanation occurs stereospecifically. The major side reactions in these cyclopropanations are allylic C–H



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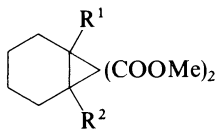
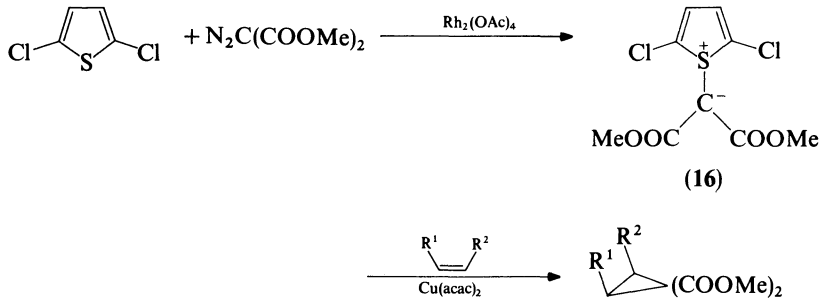


$R^1 = R^2 = H$	63.7%	+	insertion products 4.7%
$R^1 = H, R^2 = Me$	29.6%		39.0%
$R^1 = R^2 = Me$	—		43.2%

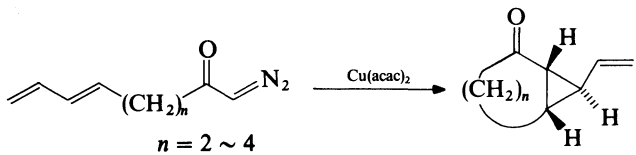
insertions and dimerization of the carbene leading to ethylenetetracarboxylic ester formation. The catalytic reactions of diazomalonic esters with olefins are relatively sensitive to steric hindrance. Thus, as steric hindrance is increased, the C–H insertion becomes increasingly important (equation 71)[329]. A stable crystalline sulfur ylide, **16**, has been shown to transfer bismethoxycarbonylmethylene to alkenes under the catalytic action of $Cu(acac)_2$ (equation 72)[330]. Bromomalonic esters with DBU/$CuBr_2$[331] as well as



(72)

dibromomalonic esters and the cyano derivatives with Cu_2Br_2[332] react with alkenes to give cyclopropanes non-stereospecifically. A non-carbenic, stereospecific cyclopropanation of alkenes with diethyl malonate is also developed (Section III.C.1)[333]. A high enantiomeric excess (e.e.) has been materialized in the cyclopropanation of styrene with 2-diazodimedone with chiral copper complexes[334]. In the photochemical reactions, diazomalononitrile cyclopropanates alkenes as well as alkynes in good yields[335].

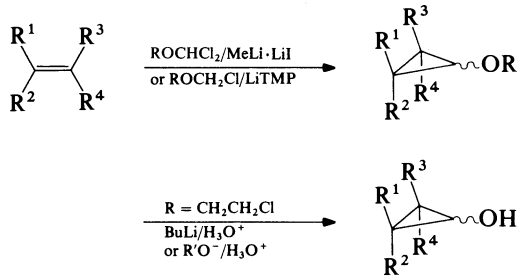
The intramolecular cyclopropanations of α-diazocarbonyl compounds have been extensively studied and recently reviewed[336]. The reaction is satisfactorily accomplished when the diazo carbon atom is proximal to the double bond in the substrate. Thus, the construction of bicyclo[3.1.0]hexane and bicyclo[4.1.0]heptane skeletons has been achieved by this method, whereas the synthesis of bicyclo[5.1.0]octane or the larger bicyclic systems has usually been difficult (equation 73). Bicyclo[2.1.0]pentan-2-ones expected in the reaction of β,γ-unsaturated diazoketones are generally labile and readily undergo the ring cleavage to give β,γ-unsaturated ketenes[337].



(73)

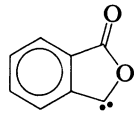
6. *Carbenes containing α-heteroatom(s) other than halogen*

Alkoxycarbenes have been generated either from $ROCHCl_2$/MeLi·LiI[338,339] or from $ROCH_2Cl$/LiTMP[340] and have been added to alkenes and alkynes in good yields. The reactions of aryloxycarbens have also been carried out in similar ways[338,341]. The additions of these carbenes to olefinic double bonds occur stereospecifically, but *syn/anti* stereoselectivities are variant. Addition of 2-chloroethoxymethylene provides a convenient route to cyclopropanols (equation 74)[160,342]. Acyloxy- and carbamoyloxycyclopropanes, which are also the precursors for cyclopropanols, have been prepared by reactions of alkenes with $RCOOCH_2Cl$/LiTMP (R = *t*-Bu, NMe_2)[343].



(74)

Chloro(methoxy)-[344] and chloro(phenoxy)carbenes[345], which are generated from the diazirine precursors, behave as ambiphiles in additions to alkenes, exhibiting high reactivities toward both electron-poor and electron-rich olefins. Methoxy(phenyl)-[346] and ferrocenyl(methoxy)methylenes[347] have been transferred in a stereospecific manner from transition metal complexes of these species to electron-deficient alkenes. Irradiation of benzocyclobutanedione with UV light induces a rearrangement of the cyclic α-diketone to **17**, which has been trapped by alkenes in good yields[348]. Thermolysis of **18** gives rise to nucleophilic dimethoxycarbene[349], which has been intercepted by electron-deficient olefins or by styrene derivatives.



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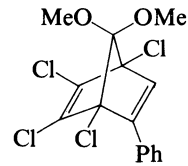


(18)

Phenylthiomethylene (:CHSPh) and chloro(phenylthio)methylene [:C(Cl)SPh] adducts have been obtained by reactions of olefins with $PhSCH_2Cl$/base[350] and $PhSCHCl_2$/base[351], respectively. Previously, strong bases such as *t*-BuOK, *n*-BuLi, and NaH have been used, but the reactions can be carried out more conveniently under PTC conditions[352], usually with better yields. The addition of phenylthiomethylene is stereospecific and gives *syn*-adducts preferentially. Similarly, phenylselenomethylene transfer from $PhSeCH_2Cl$/base is found to be stereospecific and *syn*-selective[353]. Bisalkylthio-[354] and bisphenylthiocarbenes[355] are generated from the tosylhydrazones of dithiocarbonic esters and from trisphenylthiomethyllithium [$(PhS)_3CLi$], respectively. These carbenes [:$C(SR)_2$, :$C(SPh)_2$] are highly electrophilic and add merely to highly electron-rich olefins such as ketene acetals and enamines.

Phenylsulfinylcarbene (:CHSOPh) generated by thermolysis of the diazo precursor exhibits remarkably high *anti*-selectivity in addition to alkenes[356]. In contrast, arylsulfonylcarbenes (:$CHSO_2Ar$), photochemically derived from the corresponding diazo compounds, show much lower stereoselectivities (equation 75)[357]. Trimethylsilylmethylene (:$CHSiMe_3$) has been transferred from Me_3SiCHN_2[358] or from Me_3SiCH_2Cl/LiTMP[359] to several alkenes in moderate yields with *anti*-selectivity. Allyl(trimethylsilyl)carbenes generated from gem-dibromo compounds with MeLi have been found to undergo intramolecular cyclization to give 1-trimethylsilylbicyclobutanes[360]. Phosphorylcarbenes [:$CRPO(OEt)_2$, (R = H, Ph)][361] as well as alkylmetal-substituted acyl- and alkoxycarbonylcarbenes [:C(M)COR, (M = HgMe, $GeMe_3$, $SnMe_3$,

(75)

Precursor	Conditions	Yield, %	*anti/syn* ratio	Ref.
$PhSCH_2Cl$	PTC	67	0.56	352
$PhSOCHN_2$	thermal	35–40	34	356
$PhSO_2CHN_2$	*hv*	48	2.1	357

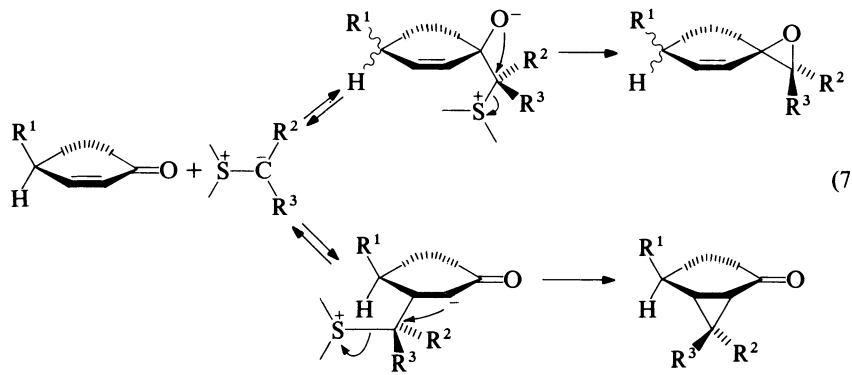
$PbMe_3$; R=Me, OR′)] have also been generated from the corresponding diazo precursors and have added to carbon–carbon multiple bonds[362].

B. Cyclopropanation of Michael Acceptors

1. With ylides

Ylides can cyclopropanate unsaturated systems which are susceptible to Michael additions, i.e. α,β-unsaturated ketones, esters, amides, nitriles, sulfones, sulfonamides, and nitro compounds[363]. Enhancement of electron withdrawal from the carbon–carbon double bond facilitates the reaction. The reaction is non-stereospecific. The intermediacy of zwitterions has generally been accepted, and hence the stereochemistry of the product may be predictable on the basis of the stepwise mechanism[363]. Namely, the Michael addition of the ylide will occur predominantly from the less hindered side of the double bond in a given molecule and the subsequent cyclization will take place in the conformation which minimizes the non-bonded repulsions.

α,β-Unsaturated carbonyl compounds are ambident in their behavior toward nucleophiles. Thus, with highly reactive ylides, the reagents preferentially undergo carbonyl addition, whereas stabilized ylides add to carbon–carbon double bond in the Michael manner (equation 76). The addition to the carbonyl group (1,2-addition) is reversible,

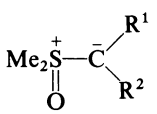


(76)

however, and therefore the cyclopropyl derivatives may be produced as the thermodynamically controlled product[363, 364]. The side reactions in this type of cyclopropanations are oxirane formation (α,β-unsaturated ketones)[365], acylation of the ylides (α,β-unsaturated

esters)[366] and γ-lactam formation (α,β-unsaturated amides)[367]. As expected, steric hindrance to the Michael addition results in enhanced carbonyl addition, whereas the stabilization of the ylide by an electron-withdrawing substituent, alkyl substitutions on the ylide carbon, and the presence of a bulky group at the carbonyl carbon favor the cyclopropane formation. These observations are consistent with the reversibility of the carbonyl addition.

Typical ylides used in the methylenation of Michael acceptors are the sulfur ylides **19**[365], **20**[368] and **21** ($R^1 = R^2 = H$)[369]. Many functional groups, such as hydroxyl, amino, nitro,



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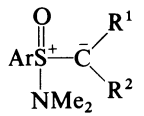

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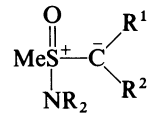

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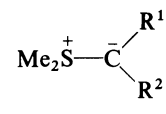
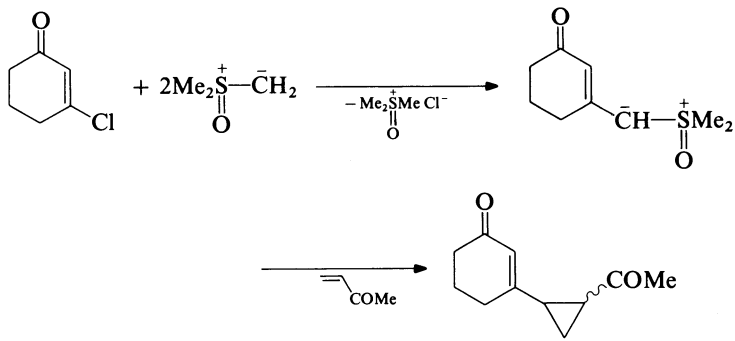


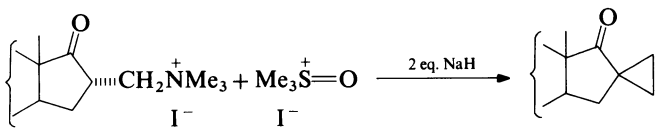
(22)

cyano, carbonyl, sulfonyl and sulfoxide, are compatible with the reaction. With excess reagent, however, the carbonyl function in aldehydes and ketones may react to form epoxides. Dimethylsulfonium methylide, **22** ($R^1 = R^2 = H$)[365], does not satisfactorily cyclopropanate the Michael acceptors owing to the preponderance of 1,2-addition (epoxide formation) except for certain α,β-unsaturated esters and sulfones[370]. Michael acceptors substituted by a good leaving group in the β-position usually do not give the methylene transferred products, since β-elimination takes place faster than the cyclization in the zwitterionic intermediate. However, the product can serve as the precursor for the vinylogously stabilized ylides and have been utilized in the cyclopropanation as shown in equation 77[371, 385].



(77)

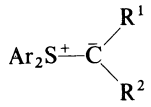
The reactions of allenic as well as of acetylenic Michael acceptors with sulfur ylides usually afford vinylogously stabilized ylides in place of the expected three-membered ring products[372]. This is due to the rapid proton shift in the zwitterionic intermediates. The *in situ* generation of the requisite Michael acceptor may be accomplished by utilizing masked enones, namely, the Mannich bases (equation 78)[373]. Since the oxosulfonium salts undergo



(78)

a facile H–D exchange, deuterium-labeled cyclopropanes are readily prepared by applying this type of cyclopropanation[374].

Mono- and dialkylmethylene transfer to Michael acceptors have satisfactorily been achieved with the readily accessible ylides **20**[368]. Dialkylmethylenes[375], including cyclopropylidenes[96], can also be transferred from the diarylsulfonium ylides, **23**, to α,β-unsaturated carbonyl compounds (equation 79). The reaction is free from complications



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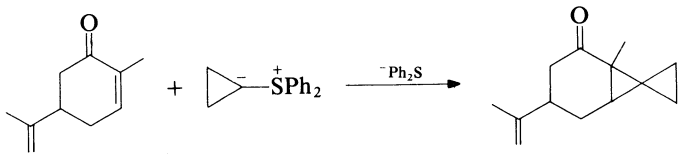
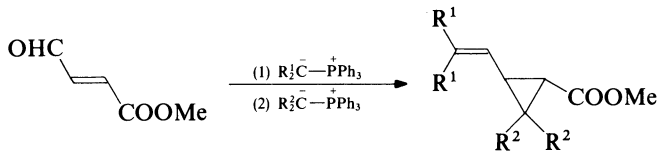


(79)

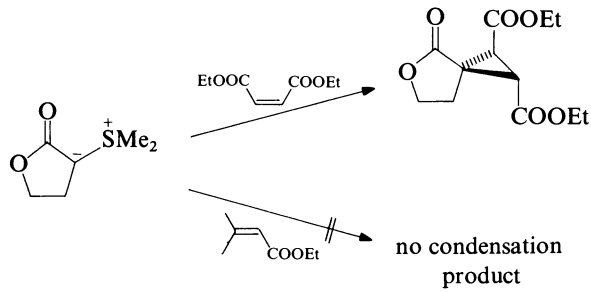
due to the carbonyl addition unless the conjugate addition is sterically hindered. Phosphorus ylides are also used to transfer dialkylmethylenes to certain α,β-unsaturated esters (equation 80)[376]. Moderately stabilized ylides, such as phenyl-[377], alkynyl-[378],



(80)

trimethylsilyl-[379], phenylthio-[380] and chloromethylides[381] have also been successfully used in the same type of reactions.

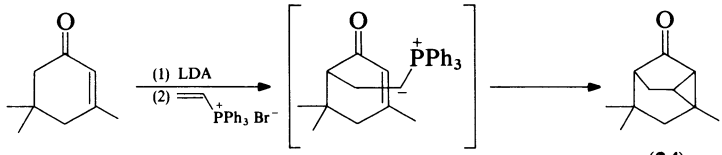
Oxosulfonium ylides as well as sulfonium ylides stabilized by an electron-withdrawing group, such as an acyl[382], an alkoxycarbonyl[383], a cyano[384] and one of their vinylogues[385] satisfactorily cyclopropanate a variety of Michael acceptors (e.g., equation 81)[383]. In these reactions, the 1,2-addition is usually a minor pathway. Ylides stabilized by two



(81)

electronegative groups, however, are usually not sufficiently reactive in cyclopropanation, even toward relative reactive Michael acceptors. Cyclopropanation by utilizing selenium ylides has also been developed[386].

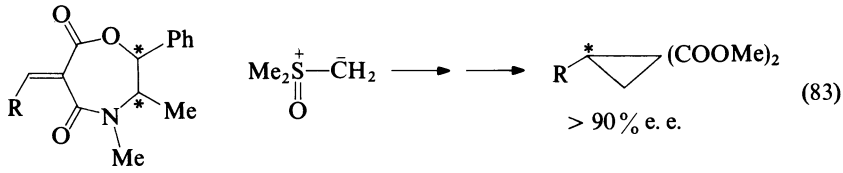
There is a report describing intramolecular, stereoselective cyclopropanations by utilizing the ylide reaction[387]. Preparation of tricyclic compounds, such as **24**, has been accomplished by intramolecular reaction of phosphorous ylide generated *in situ* by addition of enolate anion to vinylphosphonium salt (equation 82)[388]. Optically active



(82)

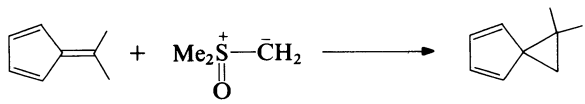
(24)

cyclopropanes have been obtained by using the optically active **20**[368, 389]. Michael acceptors carrying a chiral substituent have been cyclopropanated with high enantioselectivities (equation 83)[390]. In addition to the usual Michael acceptors, conjugated



(83)

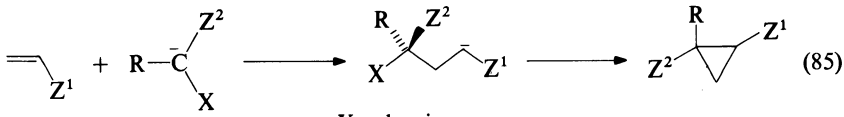
dienes, such as 1,3-butadiene[391], vinylpyridines[392], fulvenes[393] and styrene derivatives[365, 394] have successfully been cyclopropanated with sulfur ylides, as exemplified in equation 84.



(84)

2. *With α-halocarbanions and related species*

When carbon nucleophiles carrying a leaving group at the α-position are allowed to react with Michael acceptors, the resultant intermediate anions will be capable of undergoing an intramolecular displacement to produce cyclopropanes (equation 85). Some reactions described in Section III. A may actually proceed in this way.

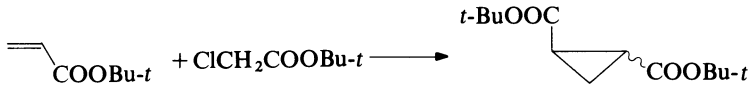


(85)

X = leaving group

The carbanions generated from α-halogenated ketones[395], esters[396, 397], nitriles[397, 398], nitro compounds[399] and sulfones[400] have been reacted with various Michael acceptors to give polyfunctionalized cyclopropanes. Some of the reactions have successfully been executed under PTC conditions[401]. The carbanions have also been generated from α,α-dihalogenated analogues with organometallic reagents[402]. The conjugate addition of nucleophiles to α-halosubstituted Michael acceptors will produce equivalent species[403]. Ammonium salts in place of halides may also be used as leaving groups[404]. It has been

observed that, in certain cases, the stereochemical course of the reaction is markedly affected by the polarity of the solvent employed (equation 86)[405]. Optically active

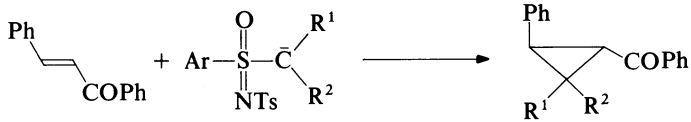


(86)

cis/trans ratio			
t-BuOK/toluene	*t*-BuOK/THF	*t*-BuOK/DMF	PTC
60/40	52/48	17/83	12/88

cyclopropanes have been obtained in the reaction of achiral Michael acceptors with α-haloesters carrying a chiral alkoxyl group[406].

Some sulfur-centered functions and a nitro group which are primarily required for stabilizing the anion, are also capable of serving as the leaving group. Thus, sulfonimidoyl-stabilized carbanions, **25**, transfer methylene as well as alkylidenes to Michael acceptors (equation 87)[407]. Phenyl sulfones (X = SO_2Ph in equation 85)[408] and nitromethane

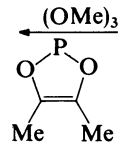


(87)

(25)

(R = Z^2 = H, X = NO_2 in equation 85)[409] have been employed for cyclopropanation of doubly activated Michael acceptors. Ketene thioacetals have been cyclopropanated by certain sulfides[410]. The construction of a tricyclo[2.2.2.$0^{3,5}$]octan-2-one skeleton, such as in **24**, has been accomplished in a one-pot reaction of substituted cyclohexenones with α-bromoacrylic esters[411] or vinyl sulfones[412].

The nucleophilicities of cyclopropenone acetals[413], bromoketene acetals[414] and an oxaphosphorane derivative, **26**[415], are high enough to enable reaction with some Michael acceptors. Thus, cyclopropaneacetic esters (e.g. equation 88), cyclopropanecarboxylic esters, and 1-acetyl-1-methylcyclopropanes have been generated, respectively, from these precursors.



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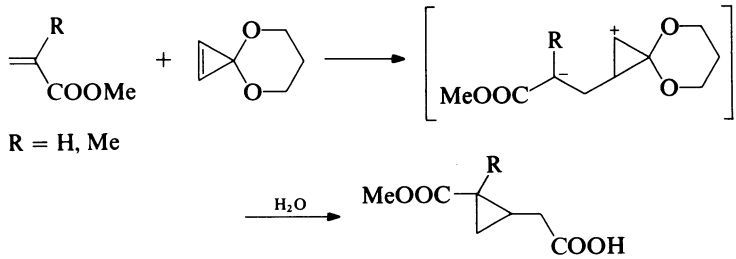


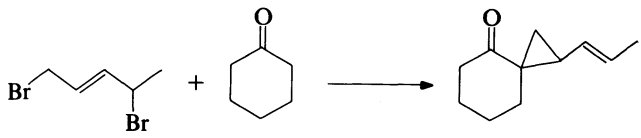
(88)

C. Cyclopropanation of Active Methylene Compounds

1. With 1,2-dihaloethanes and related compounds

The preparation of cyclopropyl compounds by a successive alkylation–cyclization of active methylene groups with 1,2-dihaloethane or its equivalents has found fairly widespread use. The cyclization step corresponds to the intramolecular displacement described in Section II. C. A major side reaction in this type of cyclopropanations is β-elimination, which takes place at the first alkylation step of the synthesis. Malonic esters and their analogues possessing a doubly activated methylene group have most satisfactorily been cyclopropanated[416]. Some reactions are conveniently carried out under PTC conditions[417]. α-Methylene groups in ketones[418,419], amides[420] and nitriles[421,422] may also be cyclopropanated. In addition, this method has successfully been applied for reactions of bis(alkylthio)methanes[423,424], cyclopentadiene and its benzo analogues[425] and 2-methyldihydro-1,3-oxazine[426]. $NaBH_4$ reduction of the product obtained in the reaction of the latter compound provides cyclopropanecarbaldehyde. Even the weakly acidic 1,4-cyclohexadiene reacts in a similar manner to give spiro[2.5]octadienes, albeit in low yield[427].

With regard to the reagents used in this type of cyclopropanation, 1,2-dibromoethane has been used most frequently. 1-Bromo-2-chloroethane, however, may give better yields in some cases[426]. 2-Chloroethylsulfonium iodide is used in the reaction of cyclic ketones to give the spiro derivatives[418]. The use of vinylogous derivatives of 1,2-dihalides allows a synthesis of vinylcyclopropanes (equation 89)[428]. (Chloromethyl)oxirane provides substituted cyclopropylmethanols (equation 90)[421,423]. Oxiranes may also be used in place of



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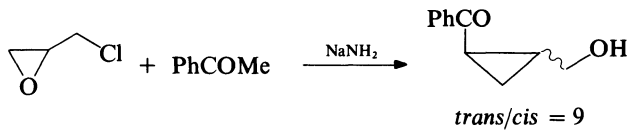
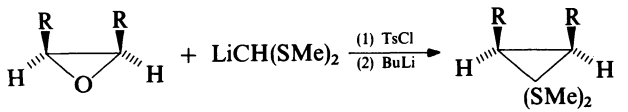


(90)

trans/cis = 9

1,2-dihalides. The intermediate alcoholate anions should be, however, converted *in situ* to the corresponding sulfonates, which allow the accomplishment of the cyclopropanation[424,429]. In these reactions, the geometry of oxiranes has been retained in the cyclopropane products (equation 91)[424]. For cyclopropanation of malonic esters, alkenes

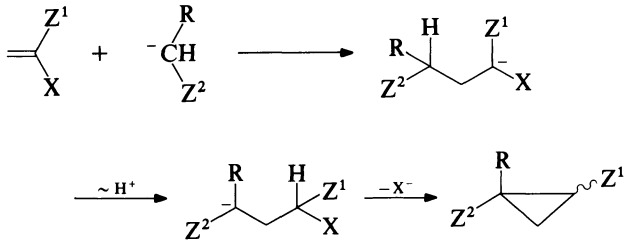


(91)

can also be utilized[359]: successive treatments of an alkene with methanesulfenyl chloride, malonate anion and dimethyl sulfate and finally with base give a cyclopropanedicarboxylic ester. The geometry of the starting alkene has been retained in the product.

2. *With Michael acceptors carrying a leaving group at the α-carbon atom*

Some Michael acceptors, which carry a good leaving group at the α-carbon atom, or whose electron-withdrawing group itself can serve as the leaving group, should be capable of giving cyclopropanes on reaction with dibasic, active methylene compounds. In this type of reaction, a prototropic shift subsequent to the Michael addition is necessary to produce the intermediate, which undergoes the intramolecular displacement reaction (equation 92).

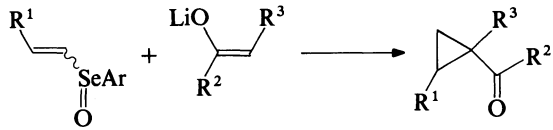


(92)

X = leaving group

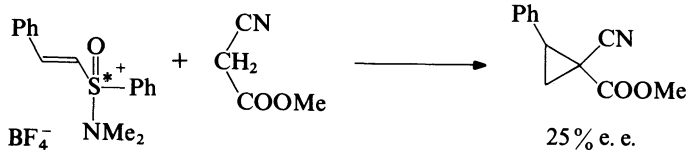
Thus, the basicity of the carbanion generated by the Michael addition should be higher than, or at least comparable to, that of the reagent nucleophile. The presence of acidic protons other than those required in the aforementioned process may complicate the reaction[430]. The formation of five-membered ring compounds in preference to three-membered ring ones has been observed in some cases[431].

A variety of α,β-unsaturated esters and nitriles bearing a leaving group at the α-carbon[432,433], vinyl selenones[434], vinylsulfoxonium salts[431] and vinylsulfonium salts[435–437] have been found to react with doubly activated methylene compounds, such as malonic esters, acyl- or cyanoacetic esters[431–436] and disulfonylmethanes[437], to give cyclopropyl derivatives. Similarly, the cyclopropanations of alkylthiomethyl ketones ($RSCH_2COR'$), α-alkylthioacetic esters ($RSCH_2COOR'$), and α-alkylthioacetonitriles ($RSCH_2CN$)[430,434,438], stabilized sulfur ylides[439,440] and nitromethane[431,434] have been achieved with vinyl selenoxide (equation 93)[438], vinylsulfonium salts[440], vinyl sulfones[430], vinyl selenones[434], or α-bromoacrylic esters[439].



(93)

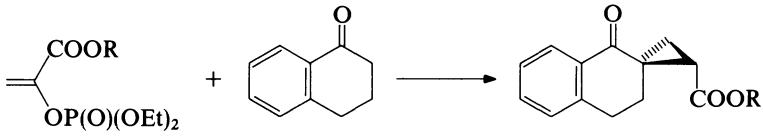
Asymmetric induction has been accomplished with the use of optically active vinylsulfonium salts with asymmetry at sulfur (equation 94)[431]. Less acidic methylene



(94)

25% e. e.

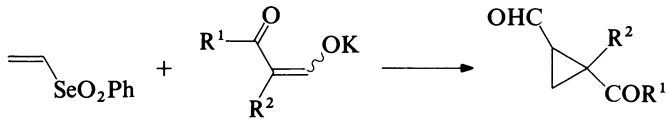
groups in ketones, carboxylic esters, nitriles and sulfones[437], as well as in cyclopentadiene and its benzo analogues[431,433], have successfully been cyclopropanated with vinyl selenoxides[438], vinylsulfonium or vinylsulfoxonium salts[436,437]. Phosphoenol pyruvates



(95)

are also utilized as the reagent (equation 95)[433]. Variant stereoselectivities observed in these reactions may be accounted for by non-bonded interactions in the cyclization step similar to those mentioned in the cyclopropanations of the Michael acceptors with ylides (Section III.B.1).

Rearrangement in the intermediates sometimes leads to unexpected products. In the reactions of the monoenolates of 1,3-diones with vinyl selenones, 2-acylcyclopropanecarbaldehydes have been obtained in good yields (equation 96)[441].

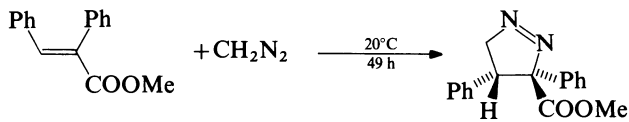


(96)

D. Cyclopropanation with Diazo Compounds via 1-Pyrazolines

Diazo compounds have widely been used in the synthesis of three-membered carbocycles either as carbene sources or as precursors for 1-pyrazolines or 3*H*-pyrazoles. The latter route is particularly valuable for the alkylmethylenation of activated multiple bonds, since alkylidenes (the former route) generally give very poor results owing to their susceptibilities to rapid intramolecular insertion reactions.

Cycloadditions of diazo compounds with unsaturated substrates giving 1-pyrazolines or 3*H*-pyrazoles have been extensively reviewed[33,442]. A concerted, and hence stereospecific, reaction mechanism is generally accepted. Substitution of the diazo carbon with electron-withdrawing groups reduces the reactivity of the diazo compounds. Thus, the reactivity toward alkenes falls off in the sequence: $N_2CMe_2 > N_2CH_2 > N_2CPh_2 > N_2CHCOOR > N_2CHCOR > N_2C(COR)_2$. On the other hand, alkenes are activated toward these 1,3-dipolar additions both by conjugation with an electron-withdrawing group (COOR, COR, CN, or SO_2R) and by substitution by an electron-donating group (OR, SR, NR_2). Conjugation of the olefinic double bond with a carbon–carbon double or triple bond as well as a ring strain also enhances the reactivity of the substrates toward attack by diazo compounds. *trans*-Olefins generally react faster than the *cis* counterparts. Acetylenes and allenes[443] are rather more reactive than the corresponding olefins. Addition of the diazo compounds to unstrained, simple alkenes is, however, usually slow and hence is not practical. This difficulty may partly be overcome by conducting the reaction under high pressure (equation 97)[444].



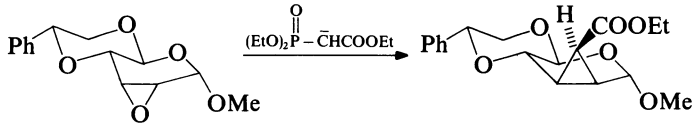
(97)

Pressure (atm)	Yield (%)
1	0
5000	66

These reactions always give 1-pyrazolines as the primary adducts. However, 1-pyrazolines may not be isolated, since they readily isomerize to 2-pyrazolines when the acidity of the C–H group adjacent to the nitrogen is sufficiently high. In some cases, nitrogen extrusion from 1-pyrazoline occurs more rapidly than the 1,3-dipolar cycloaddition, and hence the 1-pyrazoline may not always be isolated. The reaction of the diazo compound with an unsymmetrically substituted multiple bond can in principle give two isomeric 1-pyrazolines, but attachment of the nucleophilic diazo carbon with the positive end of the polarized unsaturated system generally predominates. Steric effects, however, often overshadow the electronic effects and the alternative mode of addition may predominate in the reactions of disubstituted diazomethanes. The nitrogen extrusion of 1-pyrazolines and 3*H*-pyrazoles giving the three-membered ring compounds has been treated in Section II.B.

E. Cyclopropane Formation from Oxiranes

Oxiranes can be converted to cyclopropanes in their reactions with certain phosphoranes or phosphonate carbanions. Reagents which can be used for this transformation have been restricted so far to those containing an anion-stabilizing substituent, such as an acyl[445], an alkoxycarbonyl[446], a cyano[447], or an alkylimino group[448]. Dichloromethylenephosphorane has also been successfully employed in the preparation of gem-dichlorocyclopropanes[449]. It has been shown that the reaction is not completely stereospecific, but proceeds primarily with inversion of configuration at both carbon atoms in the oxirane ring[450]. An example is given in equation 98[446].

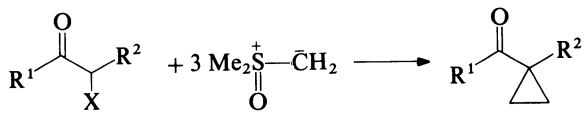


(98)

The oxirane rings in 3,4-epoxychromanes and 1,2-epoxytetrahydronaphthalenes have been converted into ethoxycarbonylcyclopropanes by reaction with ethyl malonate anion[451]. These transformations, however, appear to lack generality. gem-Dichlorocyclopropanes have been obtained from oxiranes under dichlorocarbene-generating PTC conditions[452]. Oxiranes can also be transformed into cyclopropanes in their reaction with active methylene compounds (Section III.C.1).

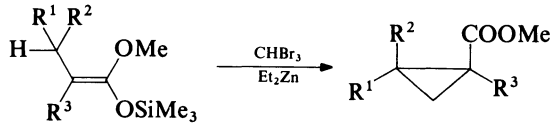
F. Miscellaneous

A variety of 1,2,3-triacyl- and 1,2,3-trisalkoxycarbonylcyclopropanes have been prepared from the corresponding acyl- or alkoxycarbonylmethylides[453], α-haloketones[454] and α-halocarboxylic esters[455]. The reactions of α-haloketones and α-halocarboxylic esters with three equivalents of sulfoxonium methylide afford cyclopropyl ketones and cyclopropanecarboxylic esters, respectively (equation 99)[456]. The reagent prepared from CH_2I_2 and Zn/Cu reacts with α-hydroxyketones to give cyclopropylmethanols[457].



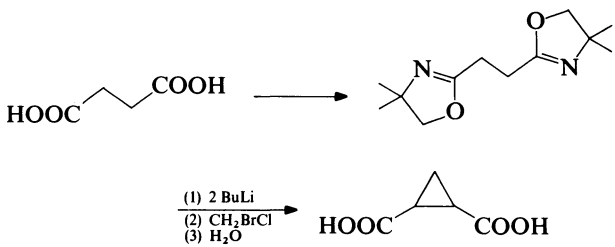
(99)

Silyl enol ethers of cycloalkanones are converted into spiro cyclopropylmethanols with $CH_2I_2/ZnEt_2$[458]. The reaction of ketene monosilyl acetals with $CHBr_3/ZnEt_2$ gives cyclopropanecarboxylic esters (equation 100)[459]. 1-Cyanocyclopropanecarboxylic esters



(100)

have been obtained in the reaction of alkenes with cyanoacetic ester in the presence of $CuCl_2/Cu(OAc)_2$[460]. Succinic acid has been converted to 1,2-cyclopropanedicarboxylic acid via a stabilized 1,2-dilithio compound (equation 101)[461]. Acrylic and methacrylic



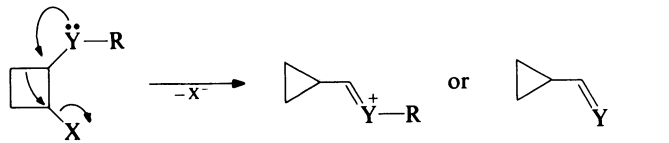
(101)

esters can be methylenated in a stepwise fashion involving a photochemical addition of CH_2Cl_2 followed by electrochemical reduction[462]. Photosensitized reaction of maleic anhydride with 2-propynyl halides affords (1-halovinyl)cyclopropane derivatives[463]. Norbornene undergoes palladium-catalyzed cyclopropanation by a variety of terminal alkynes as well as with 1-bromo-1-alkenes[464].

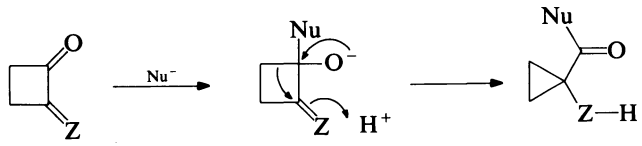
IV. REARRANGEMENT REACTIONS

A. Ring Contractions of Cyclobutyl Derivatives

Cyclobutanes vicinally substituted by an electron-donating group and a leaving group, or their equivalent such as an oxo group, undergo facile ring contractions to give cyclopropyl derivatives (equations 102 and 103)[465]. Compounds capable of undergoing



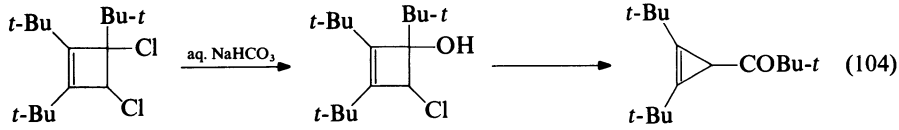
(102)



(103)

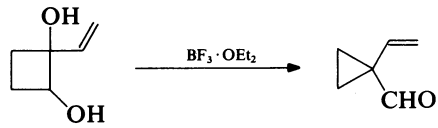
this type of transformation include 2-substituted cyclobutanols, α-substituted cyclobutanones and the corresponding acetals, 1,2-cyclobutanediones, 2-alkylidenecyclobutanols and 1,2-epoxycyclobutanes. The ring contraction is generally stereospecific with inversion of configuration at the carbon bearing the leaving group. The reaction is believed to proceed via a conformation in which the leaving group adopts a pseudo-equatorial position.

Cyclobutanols substituted by a leaving group at the 2-position are transformed into cyclopropanecarbaldehydes or cyclopropyl ketones upon treatment with base[466]. The reaction of a 3,4-dichlorocyclobutene derivative with aqueous base to give a 2-cyclopropen-1-yl ketone probably proceeds via a 4-chlorocyclobut-2-en-1-ol (equation 104)[467]. In the oxidation of 1-methylcyclobutene with metallic salts in aqueous medium to



(104)

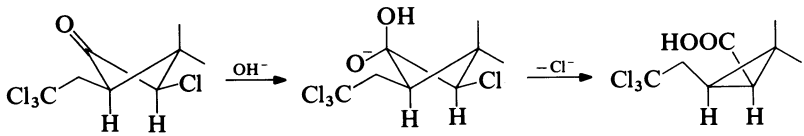
produce cyclopropyl methyl ketone, a ring contraction of a cyclobutyl intermediate has been proposed[468]. 2-Halocyclobutylamines generated *in situ* by the LAH reduction of the corresponding azides have analogously been converted into cyclopropylmethylamines[469]. 1,2-Cyclobutanediols are also transformed into cyclopropyl carbonyl compounds either under the acidic conditions (equation 105) or by pyrolysis at 220–300°C[470]. The *trans*-diol



(105)

usually rearranges more rapidly than the *cis* counterpart. In the reaction of monoalkylated compounds, the tertiary hydroxyl group is the preferred, if not the exclusive, leaving group.

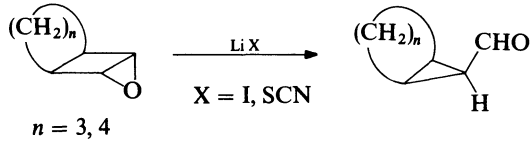
The ring contraction of α-substituted cyclobutanones, which are readily prepared by the reactions of chloroketenes with alkenes or by the acyloin condensation of succinic esters, provides cyclopropanecarboxylic acids and their derivatives[471]. The rearrangements are brought about by nucleophilic reagents, such as aqueous Na_2CO_3, ethanolic NaOEt, Grignard reagents and ammonia. The rearrangement occurs stereospecifically with inversion of configuration at the α-carbon atom[472], but epimerization at this carbon prior to the rearrangement may complicate the stereochemical consequence of the transformation[473]. Cyclobutoxide anions generated by the addition of the nucleophiles to the cyclobutanone carbonyl group are believed to be the intermediates (equation 106).



(106)

Application of the silver ion-promoted reaction of 2-chlorobutanones allows one to carry out the rearrangement under neutral conditions[474]. Irradiation of 2-chlorocyclobutanones with UV light in methanol induces an analogous rearrangement, but this photoreaction lacks stereospecificity[475].

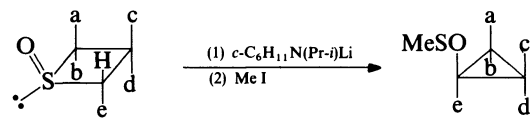
The ring contraction of 1,2-cyclobutanediones is promoted either by acids or by bases in protic media[476]. The reaction products are α-hydroxycyclopropanecarboxylic acids or the corresponding esters. Rearrangements of some 2-alkylidenecyclobutanols to cyclopropyl carbonyl compounds are also known. 1,2-Epoxycyclobutanes afford cyclopropanecarbaldehydes or cyclopropyl ketones under the catalytic action of protic acids[477], lithium iodide or lithium thiocyanate (equation 107)[478]. Under the latter conditions, the reaction



(107)

apparently proceeds with retention of configuration at the carbon atom which ends up as the α-carbon of the carbonyl product.

Certain cyclobutyl derivatives undergo Wagner–Meerwein rearrangement to cyclopropyl derivatives[129]. The silver acetate-promoted ring contraction of cyclobutyl bromides, which are specifically substituted by an electron-withdrawing group at the 1-position, gives cyclopropylmethyl acetate derivatives[479]. Certain 4-cyclopropylbutenolides have been obtained in the acid-catalyzed rearrangement of bicyclic pentanolides[480]. Thietan-1-oxides give cyclopropyl sulfoxides upon treatment with strong bases (equation 108)[481]. The reaction proceeds stereospecifically with respect to the configurations at

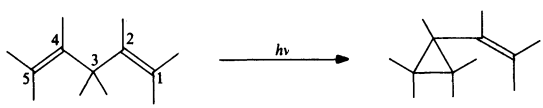


(108)

sulfur, at the migrating group, and at the migration terminus. An example of the Wolff rearrangement giving three-membered carbocycles has also been reported[482]. Transient cyclobutylidenes have been proposed to collapse to methylenecyclopropanes[483].

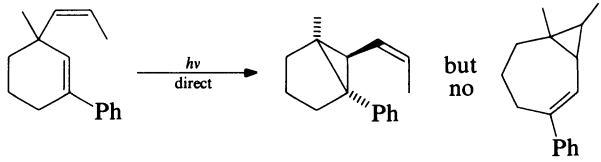
B. Other Photochemical and Thermal Rearrangements

Irradiation of certain non-conjugated dienes having two π moieties bound to a single saturated carbon atom (i.e. the di-π-methane system) with UV light results in the migration of one π moiety originally bonded to the saturated carbon, C(3), to C(4) with concomitant three-membered ring formation (equation 109)[484]. The di-π-methane rearrangement generally occurs most efficiently from the triplet excited states of cyclic dienes, where rotation about the π bonds is prohibited. In contrast, when the π-system is structurally unconstrained, and geometrical isomerization about the π bonds is possible, merely the singlet excited states can lead to efficient formation of rearranged products. A high



(109)

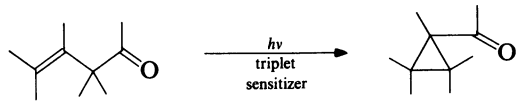
stereospecificity has been observed in the reactions of the singlet manifold. In the reaction of an unsymmetric di-π-methane system, the less terminally substituted π moiety migrates in preference to the more substituted one (equation 110). Substitution of the central, saturated carbon atom have a pronounced effect on the reactivity. Systems lacking such



(110)

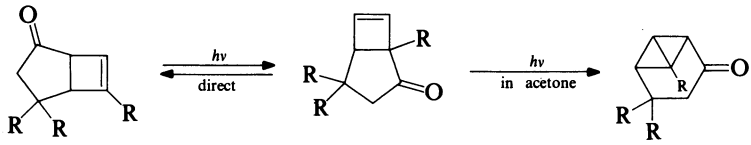
substitution undergo the rearrangement rather reluctantly. An aromatic nucleus also readily participates in the di-π-methane rearrangement.

β,γ-Unsaturated ketones undergo a photochemical transformation to acylcyclopropanes which is formally analogous to the di-π-methane rearrangement (oxa-di-π-methane rearrangement)[484-487]. This rearrangement is known to occur from the triplet excited states of the unsaturated ketones (equation 111). The direct irradiation often fails to give



(111)

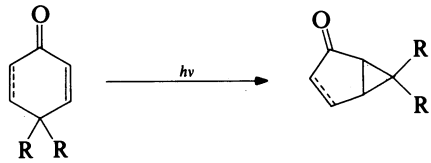
the acylcyclopropanes. The majority of the oxa-di-π-methane rearrangements has been observed so far for cyclic β,γ-unsaturated ketones, in which the rotation about the alkene moiety to the perpendicular geometry is structurally constrained (equation 112). Acyclic



(112)

R = H, Me

β,γ-unsaturated ketones tend to give products from reactions other than the oxa-di-π-methane process. In the reaction of β,γ-unsaturated aldehydes, decarbonylation generally predominates. It has been known that 2-cyclohexenones[487,488] and cross-conjugated 2,5-cyclohexadienones[488,489] photochemically rearrange stereospecifically to bicyclo[3.1.0]hexan-2-ones and bicyclo[3.1.0]hex-2-en-4-ones, respectively (equation 113).

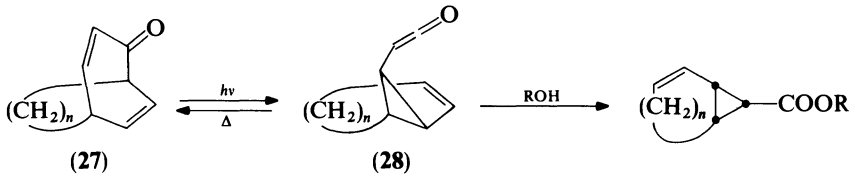


(113)

Irradiation of allylic chlorides with UV light affords cyclopropyl chlorides[490]. The rearrangements are usually slow, but the yields of the cyclopropyl products based on the consumed amounts of allyl chlorides are relatively high. Allylic Grignard reagents undergo analogous transformation upon irradiation to give cyclopropyl Grignard reagents[491]. These rearrangements are formulated as a 1,2-shift of the substituent with a concomitant C(1)–C(3) bond formation.

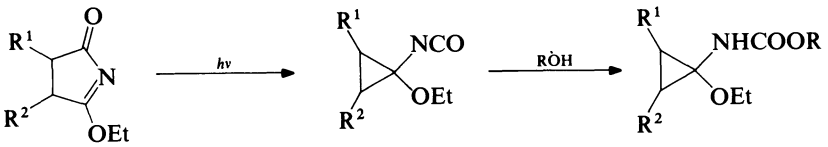
Bicyclo[3.2.*n*]alkadienones, **27** (*n* = 0–2), undergo facile [3.3] sigmatropic shift upon direct irradiation with UV light. The ketene products, **28**, thermally revert to the starting

dienones unless they are intercepted by alcohol (equation 114)[486, 487, 492]. 5-Substituted 2-cyclopentenones[493], the keto imino ether derivatives of succinimides, **29** (equation 115)[494], and 2-amino-3-alkoxycarbonyl-4,5-dihydrofurans[495] undergo photochemical



(27) (28)

(114)

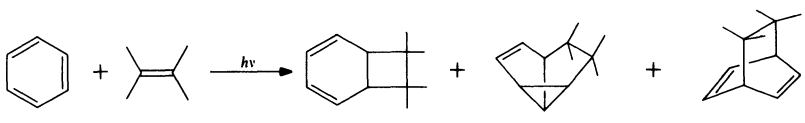


(29)

(115)

ring contractions to give cyclopropylketenes, 1-alkoxycyclopropyl isocyanates and 1,1-cyclopropanedicarboxylic acid derivatives, respectively.

Photochemical 1,3-addition of simple alkenes or enol ethers to benzene produce dihydrosemibullvalene derivatives, **30** (equation 116)[496]. Both 1,2- and 1,4-additions occur

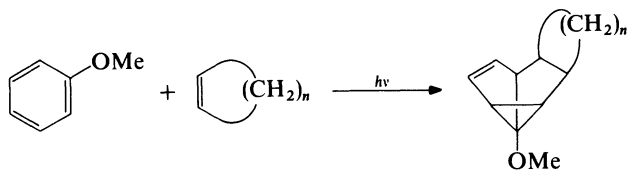


1,2- 1,3- 1,4-addition product

(30)

(116)

concurrently to varying extents. The stereochemistry of the alkenes is preserved and *endo* adducts have predominantly been formed in many cases. Electron-poor dienophilic olefins usually yield 1,2-photoadducts exclusively. The regiospecific 1,3-addition of alkenes to anisole (equation 117)[497] and to benzonitrile[498] have also been reported. Certain 1,3,5-hexatrienes, which can be generated *in situ* from 1,3-cyclohexadienes by pericyclic

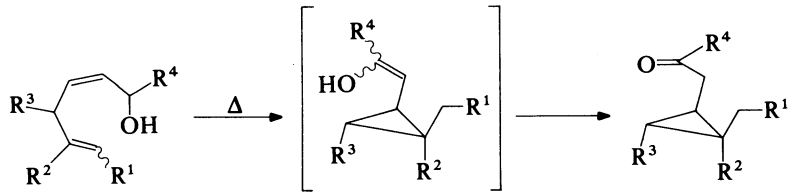


(117)

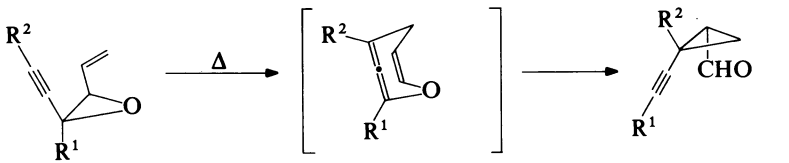
reactions, cyclize photochemically to bicyclo[3.1.0]hex-2-enes[499, 500]. The reactions are stereospecific[499], but *cis–trans* isomerization of the precursors usually competes with the

cyclization. Norbornadienes are well known to undergo intramolecular cycloaddition upon irradiation to give quadricyclanes[501].

Vapor phase thermolysis of 2,5-hexadien-1-ols at 260°C affords cyclopropylmethyl ketones[502]. The reaction has been proposed to proceed via homodienyl migration of hydrogen and is stereospecific (equation 118). 1-(1-Alkynyl)-2-vinyloxiranes undergo successive Cope rearrangements at 300–350°C to give 2-(1-alkynyl)cyclopropanecarbaldehydes (equation 119)[503]. Acid-catalyzed intramolecular acetalization followed by



(118)



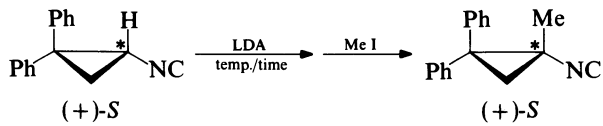
(119)

dehydration transforms *cis*-6-oxo-2-hexenols to 2-vinylcyclopropyl ketones[504]. The intermediate of this transformation will be 4,7-dihydrooxepin.

V. TRANSFORMATIONS OF CYCLOPROPYL DERIVATIVES

A. Organometallics

The derivatization of cyclopropyl compounds by substitution at the ring is generally carried out via organometallic intermediates. This is because nucleophilic substitution of cyclopropyl derivatives is usually slow unless the reaction center is substituted by a strong cation-stabilizing group, such as an alkoxyl, an alkylthio, or dimethylamino. Moreover, since cyclopropyl organometallic derivatives are usually structurally stable[505], their transformation without cleavage of the three-membered ring is possible. This structural stability is in contrast to the fact that cyclopropylmethyl organometallic compounds tend to produce the ring-opened, rearranged organometallics[506]. The cyclopropyl anion is configurationally stable as well[507] unless it is substituted by an anion-stabilizing group at the anionic center (cf. equation 120)[508–510].

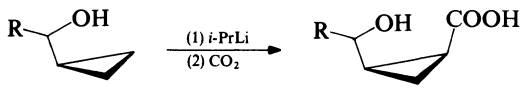


(+)-*S* (+)-*S*

(120)

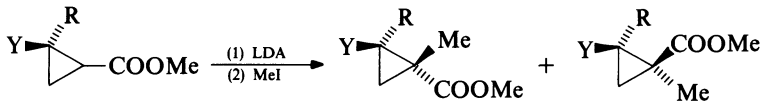
temp. (°C)	time	optical purity (%)[508]
−72±2	30 min	98
−5±1	30 min	0.3

However, direct metalation of unactivated cyclopropanes is not practical. Phenyl-[511] and (1-alkynyl)cyclopropanes[512] have been metalated at the 1-position with BuLi/*t*-BuOK and BuLi, respectively. Cyclopropylmethanols undergo preferential *syn*-lithiation with *i*-PrLi as shown in equation 121[513]. In the reaction of bridged compounds carrying a



(121)

cyclopropylmethanol moiety, the bridgehead proton adjacent to the hydroxyl group has selectively been metalated. Proton abstraction from methylenecyclopropane with BuLi predominantly occurs at the ring proton[514]. The remarkably acidic, olefinic protons in cyclopropenes are readily replaced by alkali metals[515]. Activated cyclopropyl compounds, such as cyclopropanecarboxylic esters[516], -carbonitriles, -isocyanides[517] and sulfides[509, 518] have been metalated with LDA or alkyllithium at the 1-position. It has been reported that the enolates of 2-alkyl- and 2-aryl-substituted cyclopropanecarboxylic esters undergo alkylation preferentially from the sterically less hindered face of the cyclopropane to give mainly the *Z* isomers. On the other hand, in the reactions of the 2-alkoxy-substituted derivatives, predominant formation of the *E* isomers (a reverse diastereoselectivity) has been observed (equation 122)[516].

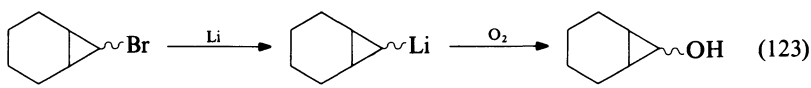


(122)

(*E*) (*Z*)

Y	R	*E*:*Z*
EtO	H	85:15
Ph	Me	21:79
t-Bu	Me	15:85

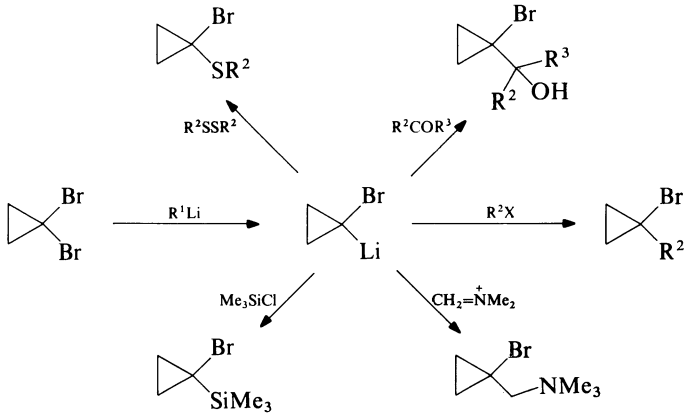
Cyclopropyllithiums and the corresponding Grignard reagents are readily prepared from the requisite cyclopropyl halides. The lithiation of cyclopropyl bromides by lithium–bromine exchange with alkyllithium proceeds with retention of configuration, whereas the lithiation by metallic lithium produces cyclopropyllithiums with almost complete loss of the stereochemistry of the starting bromides[519]. Cyclopropyllithiums have been further converted into the corresponding cuprates, which are used both in conjugate addition to enones[520] and in coupling reactions with acyl halides[521]. Cyclopropyl cuprates have also been prepared directly from the bromides and used for alkylation of the cyclopropyl derivatives with retention of configuration[522]. Oxidation of the cyclopropyllithiums with molecular oxygen produces cyclopropanols (equation 123)[523]. A generation of 2-methoxycyclopropyllithium which avoids elimination of lithium methoxide has been achieved by lithium–bromine exchange at low temperature[524].



(123)

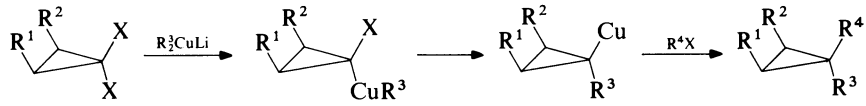
endo/*exo* = 7/2 *endo*/*exo* = 3/4

Treatment of *gem*-dibromocyclopropanes with one equivalent of alkyllithium at low temperature generates 1-bromocyclopropyllithiums, which have proved to be very versatile intermediates for the synthesis of various cyclopropyl derivatives. Thus, the reactions of the bromolithium compounds with disulfides[525], ketones[526], alkyl halides[527,528], methyleneammonium salts[529] and trimethylsilyl chloride[510] provide the corresponding 1-bromocyclopropyl derivatives (equation 124). A neighbouring ether



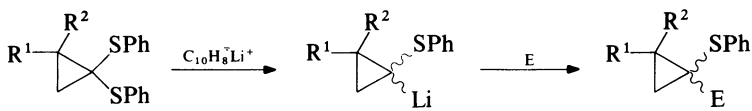
(124)

function directs the bromine–lithium exchange to the bromine *syn* to the ether residue[530]. Procedures for carrying out an *endo*-selective monoalkylation[527] and a stereoselective, successive dialkylation of the dibromocyclopropanes have also been developed (equation 125)[531]. Dialkylation of cyclopropane dihalides can also be accomplished with dialkylcuprates[532]. Methylenecyclopropanes have been prepared from the dibromocyclopropanes by utilizing the Peterson olefination reactions[510, 533, 534]. Cyclopropyl selenides,



(125)

including 1,1-diselenides, readily undergo a selenium–lithium exchange upon treatment with alkyllithium[534–536]. 1-Vinylcyclopropyllithiums generated from the 1-vinyl selenides react regioselectively with electrophiles at the ring carbon atom[536]. The reductive lithiation of cyclopropyl phenyl sulfides has been accomplished with lithium naphthalenides (equation 126)[537–539]. 1-Methoxy-[537] and 1-trimethylsilylcyclopropyl sulfides[538] as well as cyclopropanone phenylthioacetals[539] have been successfully lithiated in this way and have been allowed to react with a variety of electrophiles.



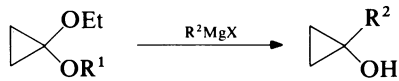
(126)

E = electrophile

B. Substitution Reactions

Cyclopropanecarboxylic acids can be converted into cyclopropyl bromides by the Hunsdiecker reaction[540]. The reaction of cyclopropyl bromides with $K_3Co(CN)_5$ produces non-stereospecifically the corresponding cyano derivatives[541]. gem-Dibromocyclopropanes also afford directly the cyano- and acetoxycyclopropanes upon treatments with $K_3Co(CN)_5$ and $Cu(OAc)_2$, respectively[541]. Trimethylsilylcyclopropane provides cyclopropyl ketones by the Friedel–Crafts reaction[542].

The substitution reactions of cyclopropanone acetals and aminals have been reviewed[543] and are discussed in Chapters 22 and 23. These compounds readily undergo the substitution with various nucleophiles, such as Grignard reagents (equation 127)[544],

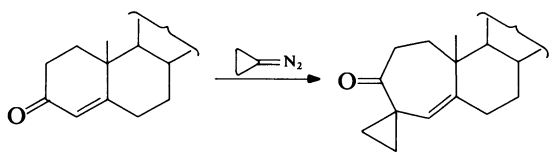


(127)

R^1 = H, Ac

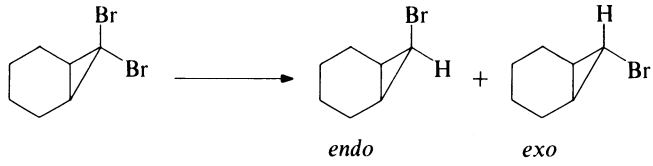
aryllithiums[545], cyanide[124, 546] and enamines[125, 547]. Reduction with metal hydrides to give cyclopropyl ethers and cyclopropylamines has also been reported[126, 548]. In these reactions, the nucleophiles generally attack the substrate from the sterically less hindered side. Acetals can usually be converted into the corresponding aminals via 1-alkoxy-substituted amines and vice versa. The condensation of the cyclopropanone aminals, or of 1-hydroxycyclopropylamines, with ketones produces the Mannich bases[549].

Diazocyclopropane can be prepared from *N*-cyclopropyl-*N*-nitrosourea or from the corresponding carbamates. Just as ordinary diazoalkanes, the cyclopropyldiazo compounds react with ketones with epoxide formation and homologation of the carbonyl compounds (equation 128)[550, 551]. Readily accessible cyclopropylidenephosphoranes provide a convenient synthetic route for methylenecyclopropanes[94, 552].



(128)

Due to the ready accessibility of gem-dihalocyclopropanes (Section III.A.4), their hydrogenolysis without cleavage of the three-membered ring is of considerable importance in the synthesis of cyclopropyl derivatives[553]. Deuterium labeling may also be accomplished by employing the appropriate reducing conditions with deuterated reagents or media. As with other organic halides, the reactivity of the cyclopropyl halides falls off in the sequences: I > Br > Cl > F, and gem-dihalides > monohalides. These trends in the reactivity enable selective reduction of mixed halides as well as a partial reduction of gem-dihalides to monohalides. For the partial reductions, *n*-Bu_3SnH[554], *n*-Bu_2SiH_2[555], LAH[556,557], Zn/ROH/KOH[558], Zn/AcOH[559], $Cr(OAc)_2$[541], MeMgBr[560], NaH/*t*-PentONa[561] and electrolysis[562] are used. A preferential formation of the sterically more congested *endo* or *cis* isomers is frequently observed, although the extents of this stereoselectivity depend on the reagent employed and the reaction conditions. The reduction of the gem-dibromides with $NaAlH_2(OCH_2CH_2OMe)_2$[563] or with $MeSOCH_2Na$[564], however, affords mainly the *exo* or *trans* isomers (equation 129). With excess reagents, *n*-Bu_3SnH and LAH as well as $NaAlH_2(OCH_2CH_2OMe)_2$ reduce the dihalides totally to the corresponding hydrocarbons. The selective hydrogenolysis of

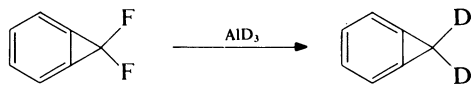


(129)

Reducing agent (*endo/exo* ratio):
n-Bu_3SnH (2.5), *n*-Bu_2SiH_2 (3.0), LAH (3.0), Zn/ROH (2.9), $Cr(OAc)_2$ (11), MeMgBr (2.2–2.7), $NaAlH_2(OCH_2CH_2OMe)_2$ (0.35), $MeSOCH_2Na$ (< 0.11), electrolysis (1.6–5.3).

geminally substituted chlorofluoro[557, 565] and bromofluoro[555, 558, 565, 566] compounds to give fluorocyclopropanes and of bromochloro derivatives to produce chlorocyclopropanes[554, 567] have been achieved with a variety of the reducing agents. In the reduction which leads to fluorocyclopropanes, the configuration of the precursor dihalo compounds is generally retained in the products, although the stereospecificity varies with the structure of the substrates, the reagents, and the reduction conditions. In the reduction of gem-bromochloro compounds, however, the stereochemical integrities of the starting compounds are largely lost.

In order to accomplish a total dehalogenation to hydrocarbons, dissolving metal reductions are most commonly employed. Cyclopropyl chlorides and bromides are satisfactorily reduced by alkali metal in alcohol[568–571] or in liquid ammonia[572]. However, the fluorides are usually resistant to the hydrogenolysis. gem-Difluorides have been

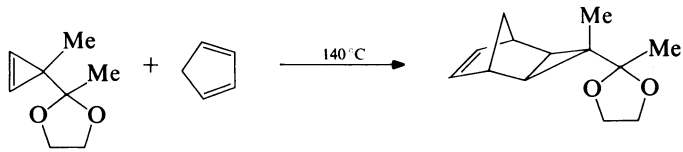


(130)

reduced with aluminum hydride (equation 130)[573]. In contrast, the catalytic hydrogenolysis is not the method of choice, since the cyclopropane ring is susceptible to a catalytic ring cleavage[568, 574].

C. Addition Reactions to Cyclopropenes

Cyclopropenes, even unactivated ones, exhibit extraordinarily high reactivity in both electrophilic and nucleophilic addition reactions. They are also good dienophiles[575] and react with a variety of conjugated dienes including acyclic 1,3-dienes[576], alicyclic 1,3-dienes[577], anthracenes and furans. An *endo* selectivity is usually observed. An alkyl or aryl substituent at the 3-position of cyclopropene sterically hinders the Diels–Alder addition and thus 3,3-dialkyl- and 3,3-diarylcyclopropenes exhibit a reduced dienophilicity (equation 131)[578, 579]. On the other hand, numerous Diels–Alder reactions have been reported for 3,3-dicyano- and 3,3-dihalocyclopropenes[575]. The reactions of 3-monosubstituted cyclopropenes with the diene take place stereoselectively from the less crowded side of the substrates (equation 132)[578, 580].



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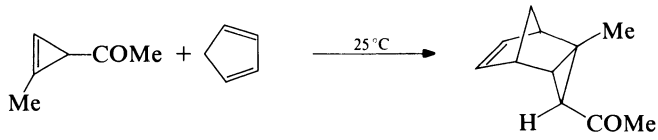
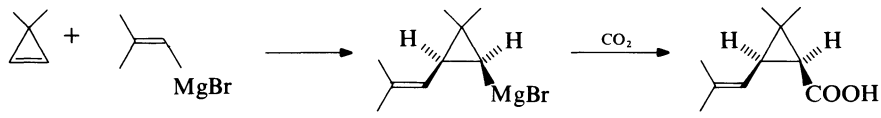


(132)

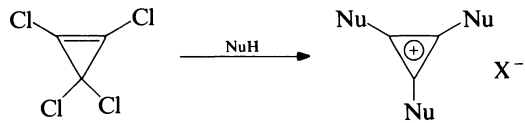
Alkyl, vinyl, and aryl Grignard reagents add to the double bond of cyclopropene in a *cis* fashion under mild conditions (equation 133)[581]. In addition, 1-alkylcyclopropenes



(133)

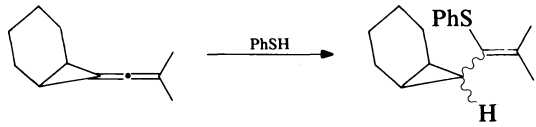
regioselectively give 2,2-disubstituted cyclopropyl Grignard reagents: i.e., the organic moiety of Grignard reagent adds to the substituted carbon atom of the ring, while Mg goes to the unsubstituted C atom. A 3-hydroxymethyl substituent directs the addition of the Grignard reagent to the side of cyclopropene *syn* to the substituent[582]. Triallylborane analogously adds to 1-methylcyclopropene in a stereospecific and regioselective manner to give *cis*-2-allyl-2-methylcyclopropylborane[583]. Hydroboration of 1-methylcyclopropene followed by oxidation with trimethylamine oxide affords *trans*-2-methylcyclopropanol[584]. Addition of other nucleophiles to the cyclopropene double bond are also known[115, 585].

Treatment of 3-chlorocyclopropenes with nucleophiles produces the substituted cyclopropenes presumably via successive addition–elimination steps[586]. Perchlorocyclopropene gives the trisubstituted cyclopropenium salts (equation 134).



(134)

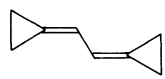
Cyclopropenes are prone to dimerize[91] and catalytic[587] as well as photochemical[588] dimerizations leading to tricyclo[3.1.0.0^{2,4}]hexane derivatives are reported. Vinylidenecyclopropanes undergo regioselective as well as stereoselective addition of thiophenol to give (1-(phenylthio)vinyl)cyclopropanes (equation 135)[589]. α-



(135)

endo/*exo* = 9

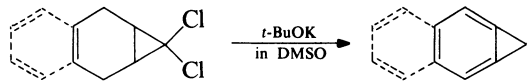
Cyclopropylidene ketones exhibit high reactivity in conjugate addition of nucleophiles[590]. Dicyclopropylideneethane, **31**[429, 591] and cyclopropylideneacetic ester[592] show high reactivities in Diels–Alder reactions.



(31)

D. Elimination Reactions

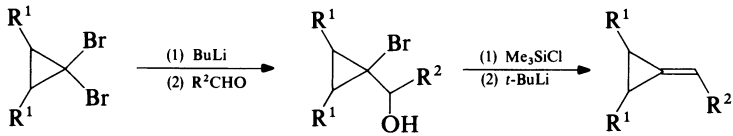
The preparation of cyclopropene derivatives by elimination of hydrogen halides, or by reductive elimination of halogens from 1,2-dihalocyclopropanes, has successfully been executed in several cases[593] but the method tends to be complicated by side reactions. The strong bases used in the elimination of hydrogen halides often add to the double bond in the produced cyclopropenes[115]. When the halocyclopropanes carry alkyl side chains, a base-catalyzed migration of the generated double bond onto the side chain takes place frequently (Section III.D.2)[594]. This double bond migration with *t*-BuOK in alkylcyclopropenes has been exploited in the synthesis of benzocyclopropene and its derivatives



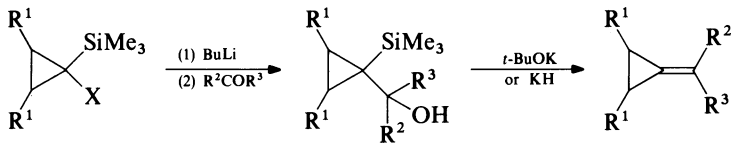
(136)

(equation 136)[595]. 1-Alkylcyclopropenes have been obtained in the reaction of gem-difluorocyclopropanes with alkyllithium by successive elimination–addition–elimination[596]. The fluoride ion-promoted elimination of 2-halo(trimethylsilyl)cyclopropanes also provides certain cyclopropenes[597].

A variety of methylenecyclopropanes have been prepared by the Peterson olefination procedures (equations 137, 138)[510, 533, 534]. 1-Alkylcyclopropyl selenides give alkylidenecyclopropanes on successive treatments with MeI/$AgClO_4$ and *t*-BuOK[598]. The adducts

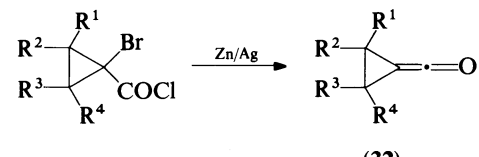


(137)



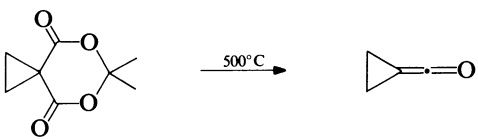
(138)

of perchlorovinylcarbene with alkenes afford cyclopropylideneacetic esters upon treatment with base[599]. The ketenes, **32**, have been generated from 1-bromocyclopropanecarbonyl chlorides with Zn/Ag[600] or by thermolysis of the spiro-Meldrum acid derivative (equation 139)[601].



(32)

(139)



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CHAPTER **8**

Organic synthesis via cyclopropanes: principles and applications

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Dedicated to Professor Siegfried Hünig on the occasion of his 65th birthday

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I. INTRODUCTION

About 100 years ago Adolf von Baeyer formulated his 'theory of ring strain', shortly after the first derivatives of cyclopropane and cyclobutane had been obtained. Although for a long period of time these classes of compounds had been regarded as laboratory curiosities, immense progress has been recorded in the past three decades in the synthesis of strained molecules. As far as cyclopropanes are concerned, this is mainly due to developments in carben(oid) chemistry. As a consequence of improving availability, the cyclopropyl moiety was increasingly regarded and utilized as a functional group participating in reactions of preparative importance. This chapter will focus on this aspect, describing 'synthetic uses' of cyclopropanes. The scope and limitations of this account are determined by three considerations:

(1) Only *isolable* cyclopropanes will be regarded.
(2) Only *opening* reactions of the cyclopropane ring will be reviewed.
(3) The products obtained should be of interest, i.e. they should be compounds of practical or theoretical purposes, or they should serve as precursors for further transformations.

Due to these restrictions mechanistic investigation of the cleavage of cyclopropanes as well as preparation of cyclopropane derivatives (see Chapter 7) will not be discussed here. Obviously the author's personal view regarding synthetic utility could not entirely be excluded and may have influenced the choice of examples presented.

Since several review articles exist on certain cyclopropyl derivatives and on various aspects of their chemistry[1-22], paragraphs dealing with these topics will mainly be restricted to newer developments. Also, synthetic use of classes of compounds described in other chapters of this book (e.g. Chapters 9, 21, 22, 23) will not be discussed here. In some

paragraphs, primary literature surveyed will mainly be confined to recent years. The literature coverage includes 1985.

The following section contains a short introduction into general reaction patterns observed with cyclopropyl derivatives, reflecting their dependency on substituent properties, as well as an overall classification of the transformations performed and analogies to related olefin reactions. Synthetic applications will be then described in Sections II–VIII which are organized according to the nature of the substituents involved. The discussion starts with more or less unactivated cyclopropanes (Section III), continues with those having heteroatoms in the α-position of a side chain (Sections IV, V), followed by cyclopropyl derivatives with heteroatoms directly linked to the three-membered ring (Section VI). Unsaturated systems like vinyl and methylene cyclopropanes are discussed in Sections VII and VIII.

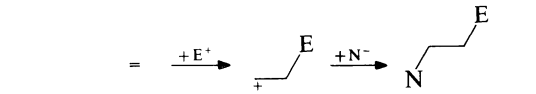
Specific examples have been chosen for each method, including reaction conditions and yields wherever possible. These are meant to reflect the synthetic utility of the transformation regarded in a representative sense; however, even when scope and limitations of these reactions are known they can not usually be discussed in much detail.

II. GENERAL REACTION PATTERNS

Strain of small rings is, in a modern way of thinking, equivalent to unique electron distribution caused by geometric restrictions. Owing to the π-type orbitals of cyclopropanes, their chemical behaviour resembles that of olefins more than that of other carbocycles[12]. This is why there is a fair analogy between the reactivity of olefins and cyclopropane derivatives. Both show pericyclic, radical, and ionic reactions in the ground state, whose occurrence and outcome, of course, will largely be dependent on functional groups, reagents and conditions. The influence of the cyclopropane substituents on geometric parameters[23] as well as on orbital properties[24, 25] have been a matter of extensive investigations, and naturally they are also very important for explaining these compounds' reactivities.

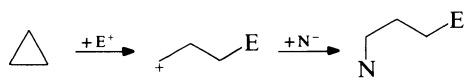
With the exception of vinylcyclopropane–cyclopentene rearrangements (cf. Section VII) radical reactions have so far rather rarely been used synthetically. This is also true for pericyclic modes of cyclopropane cleavage which are mainly restricted to divinylcyclopropane–cycloheptadiene type expansions. Cycloadditions, whether concerted or stepwise, occur only with very specific compounds[26].

The overwhelming number of reactions presented in this account proceed via polar intermediates (or at least via transition states with large charge separation). This fact enables a simple classification of these reactions (equations 2–12): attack of nucleophiles N^- or electrophiles E^+ on cyclopropanes is usually supported by electron acceptor A and electron donor D substituents, respectively, or by nucleofugal leaving groups LG. Comparison of equation 1 and equations 2–4 clearly demonstrates the close relationship



(1)

normal olefin reactivity



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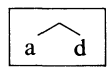
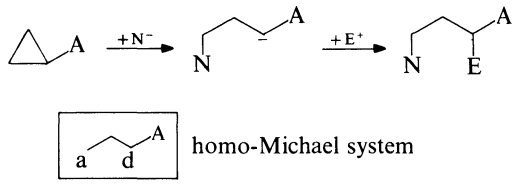


homoolefin



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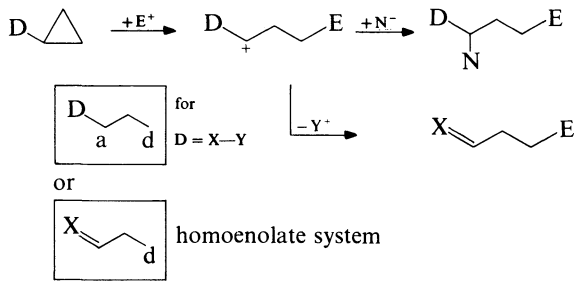
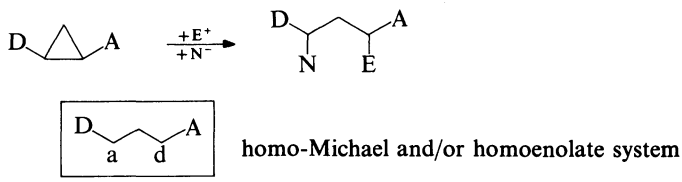


(4)

to olefin reactivity and justifies the simple picture of cyclopropanes as homoolefins. Where electrophiles E^+ and nucleophiles N^- are involved, the very helpful notation of Seebach classifying the *synthon* is presented in a separate box[11].

In the Seebach terminology cyclopropanes correspond to synthons having acceptor properties a and donor properties d respectively in a 1,3 distance, whereas the 'normal' 1,2 relationship is valid for olefins. Many synthetic methods with umpolung use this



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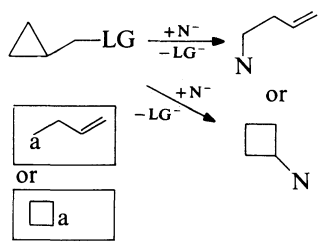

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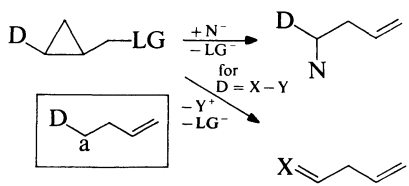

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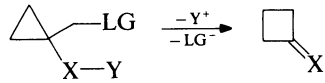
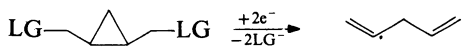


(8)

cyclopropane 'trick', allowing for instance homo-Michael reactions (equation 3), homoenolate additions (equation 4) or homoallyl substitutions (equation 6).

Usually, application of donor–acceptor-substituted derivatives not only affects ring-opening under milder conditions, but also generates products containing additional functionality for further operations (equations 5, 7, 8). Reductive or electrocyclic ring-opening can afford 1,4-dienes (equation 9) or allyl substituted products (equation 10).



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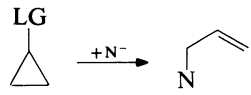

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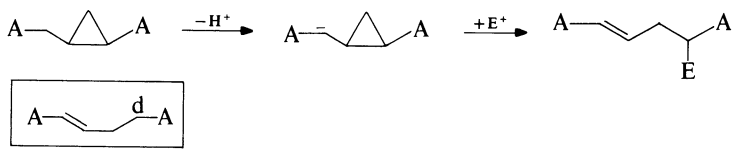


(11)

(12)

A group with donor quality can also be created by deprotonation of an α-acceptor-substituted derivative; combined with the presence of a suitable acceptor or leaving group it brings about ring cleavage as depicted in equations 11 and 12.

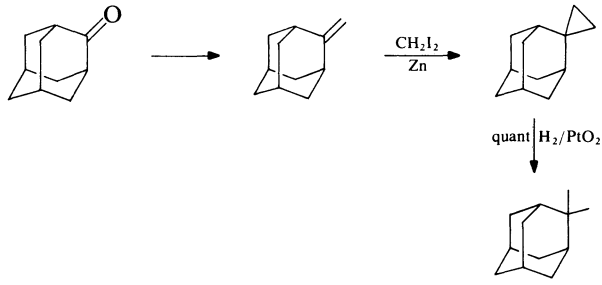
These very formal rules should help in understanding most of the reactions described in the next sections, provided that the difference in the properties of the substituents and the nature of attacking reagent (catalyst) are taken into account.

III. UNACTIVATED CYCLOPROPANES

Rather strong conditions are usually necessary to cleave cyclopropanes lacking activation by donor or acceptor substituents. This is why only two reaction types can transform this class into synthetically significant products.

A. Hydrogenolysis of Cyclopropanes

Catalytic hydrogenation of alkyl-substituted cyclopropanes usually breaks the least hindered bond[27–29]. This constitutes a nice method for converting ketones into geminal dimethyl compounds (equation 13)[30], a principle realized for the syntheses of natural[31–33] and unnatural[34] products.

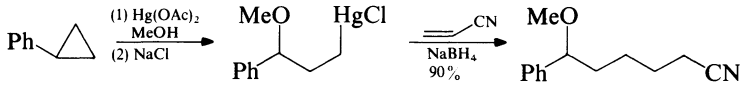


(13)

In a similar way an isopropenyl substituent can be transformed to a *t*-butyl group by cyclopropanation and hydrogenolysis[30]. The regiochemistry in the ring-opening of cyclopropanes bearing other substituents (e.g. acceptor or donor groups) has also been studied[35].

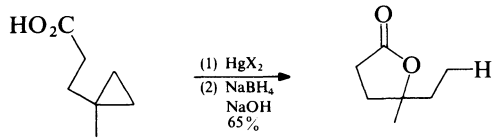
B. Reactions with Strong Electrophiles

Unactivated cyclopropanes can be cleaved by strongly electrophilic reagents like the proton, halogens or certain metal ions, unfortunately often with low regioselectivity only[36]. So far, only mercury(II)-induced openings have been of synthetic value. They incorporate suitable nucleophiles and reduction of the products can form radicals capable of additions to electrophilic olefins (equation 14)[37–39].



(14)

Intramolecular capture of the nucleophile provides heterocycles (equation 15). The regio- and stereoselectivity of this process, which is highly dependent on the substrates and conditions, have been investigated[40].



(15)

IV. α-HETEROSUBSTITUTED CYCLOPROPANES

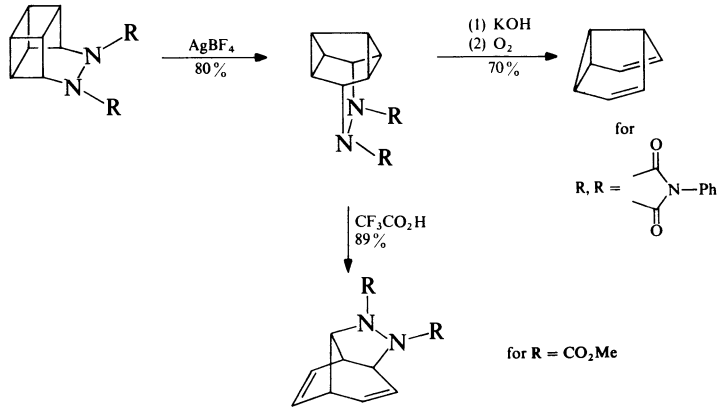
A. Silicon as Heteroatom

(Cyclopropylmethyl)trimethyl silanes can be regarded as homoallyl silanes[41]. Due to harsh conditions and incomplete regioselectivity in their reactions with strong electrophiles[42] they have so far not been referred to as reagents for synthetic problems.

B. Nitrogen as Heteroatom

Most reactions in this category are due to the interest in molecules like semibullvalene. The Paquette synthesis[43] of the parent compound takes advantage of an easy 1,5-

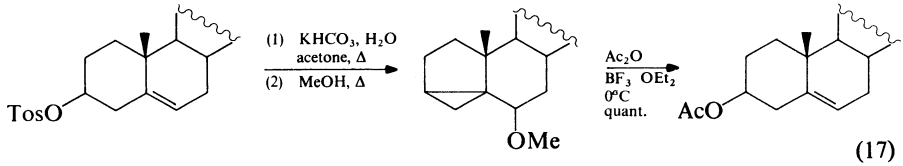
homoelimination of nitrogen as described in equation 16. This process has been applied to many substituted semibullvalenes[44-48] and to homotropilidenes[49]. If treated with acid, the biscyclopropane undergoes rearrangement to a different heterocycle[50].



(16)

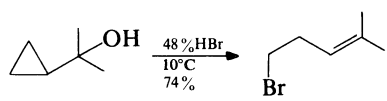
C. Oxygen and Halogens as Heteroatoms

A unique use of the cyclopropane moiety as a protecting group for the 5,6-double bond in steroids and its deprotection by an acid-induced cyclopropylcarbinyl–homoallyl rearrangement is shown in equation 17[51].



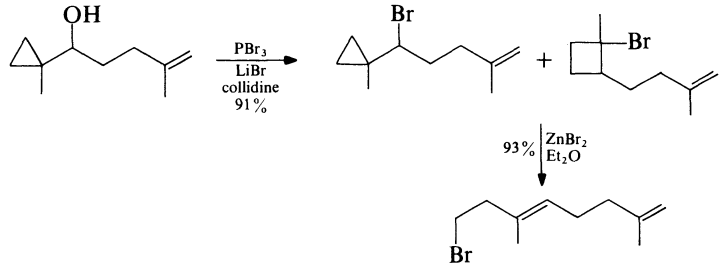
(17)

This rearrangement also occurs in the Julia synthesis of homoallyl bromides starting with easily available cyclopropylmethyl alcohols (equation 18)[52, 53]. These bromides are versatile electrophiles and have been involved as building blocks in many natural product preparations[54].

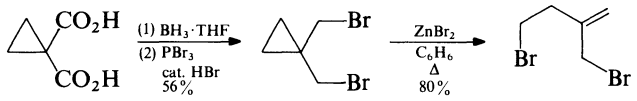


(18)

A variation employing $PBr_3/ZnBr_2$ improves stereoselectivity of this process (equation 19)[55]. Recently, several other metal salts have been tested for this purpose[56]. A bifunctional electrophile prepared as outlined in equation 20 was used in an elegant approach to morphine alkaloids[57].

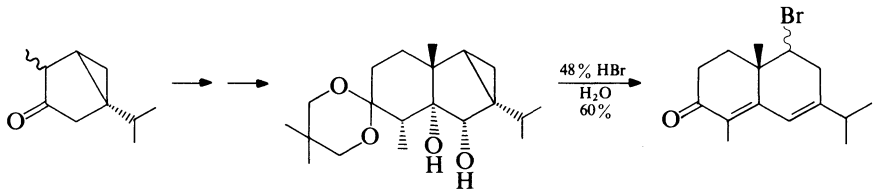


(19)



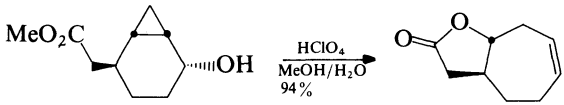
(20)

One key step in a recent steganone synthesis is a 7 → 8 ring enlargement by a cyclopropylcarbinyl–homoallyl rearrangement[58]. A 1,4-transposition of heteroatoms (HO → Br) has been brought about in a 'chiral pool' approach to certain terpenoids with thujone as readily available, optically active starting material (equation 21)[59–62].



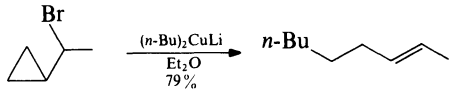
(21)

Intramolecular delivery of the nucleophile can provide a stereoselective entry to bicyclic lactones as demonstrated in equation 22; an isomeric precursor affords the corresponding *cis*-lactone[63].



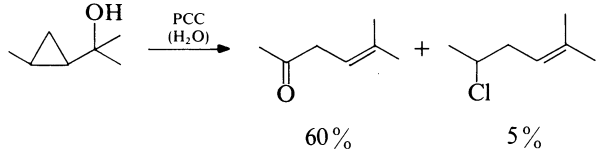
(22)

Homoallylic nucleophilic substitution is known (equation 23), but its synthetic utility is hampered by competing direct substitution without opening of the cyclopropane ring. The product ratio is largely influenced by the nature of the attacking nucleophile and the cyclopropane substituents (steric effects)[64].



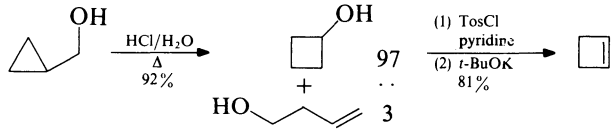
(23)

Oxidative ring-opening with pyridinium chlorochromate (PCC) gives β,γ-unsaturated ketones (equation 24). Formation of chlorinated byproducts could be suppressed by employing certain additives ($AgNO_3$, H_2O)[65]. However, bicyclic cyclopropanes afford only moderate yields.

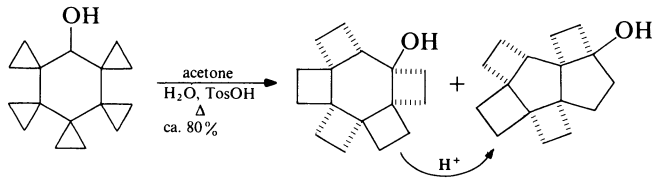


(24)

Ring expansion of cyclopropylcarbinol to cyclobutanol[66] is the basis of an efficient cyclobutene synthesis (equation 25)[67]. An elegant approach to polycyclic hydrocarbons is realized by a cascade of cyclopropylcarbinyl–cyclobutyl rearrangements (equation 26)[68].

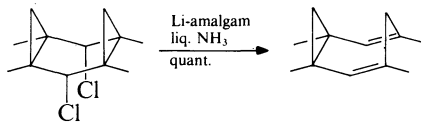


(25)



(26)

Two leaving groups which are required for 1,5-homoelimination (see equation 16) are involved in the reductive process generating homotropilidenes (equation 27)[69, 70]. Similar reactions with diols or a dimesylate as starting materials apply P_2I_4[71, 72] or NaI[73] as reducing agents and afford 1,4-dienes in variable yields.

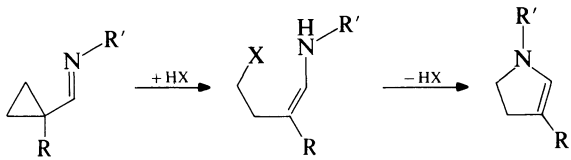


(27)

V. CYCLOPROPANES WITH IMINO, CYANO AND CARBONYL SUBSTITUENTS

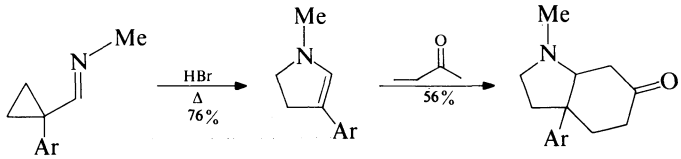
A. Imino- and Cyano-substituted Cyclopropanes

Cyclopropylimines can be transformed to dihydropyrrols by heating with catalytic amounts of acids having nucleophilic anions (Cloke rearrangement[74]). It is very likely that this ring expansion involves an acid-assisted nucleophilic attack followed by reclosure to the heterocycle as depicted in equation 28.

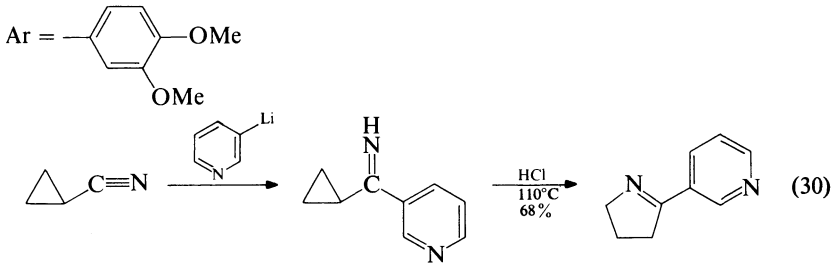


(28)

This reaction has been developed by Stevens for a refined access to various alkaloid families. Equation 29 shows the short synthesis of mesembrine, where methyl vinyl ketone is annulated to the endocyclic enamine. The precursors for the imines are usually cyclopropyl aldehydes and the corresponding amines or cyclopropyl nitriles combined with suitable organometallics as demonstrated in a simple myosmine synthesis (equation 30). Additional examples will not be discussed here since excellent review articles exist on this topic[8, 9].

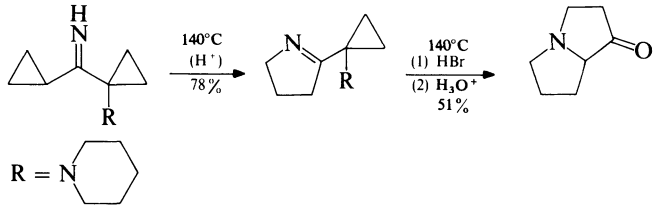


(29)



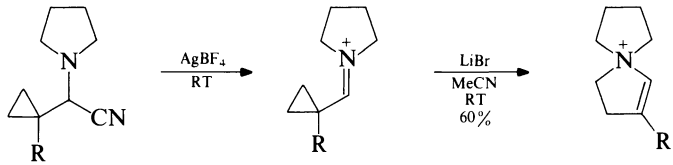
(30)

Recently, dicyclopropyl ketimines, which allow preparation of pyrrolizidinones, have been investigated (equation 31)[75]. The example depicted demonstrates that the cyclopropane ring with the piperidino group is considerably slower in the ring enlargement and therefore needs more drastic conditions (equimolar amounts of HBr) to occur.



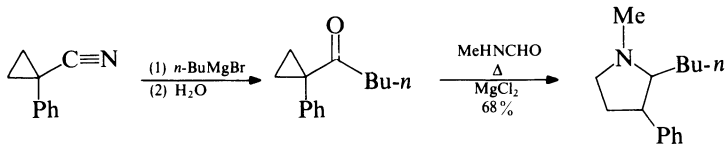
(31)

A promising alternative to generate cyclopropyl iminium ions, the presumable first intermediates in the Cloke rearrangement, is outlined in equation 32[76]. The enammonium salts have been obtained at *room temperature* after treatment with lithium bromide in acetonitrile. These very mild conditions should be compatible with many sensitive functional groups.



(32)

As mentioned above, cyanocyclopropanes are frequently used precursors for imines (see equation 30). A recent pyrrolidine synthesis which involves an *in situ* reduction of the intermediate dihydropyrrole by formic acid follows these lines (equation 33)[77].



(33)

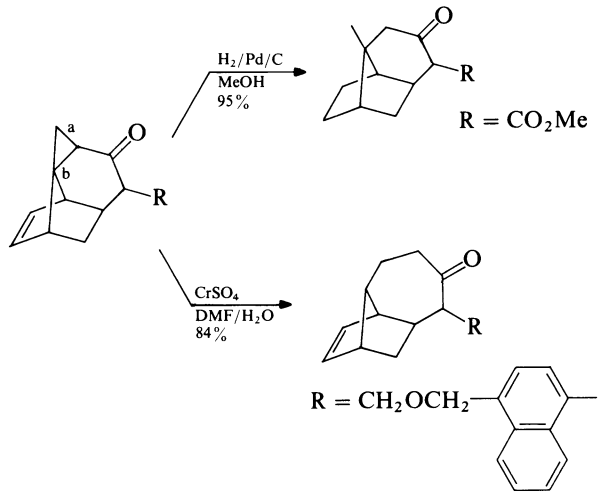
Nucleophiles can usually open only cyanocyclopropanes linked with a second acceptor group[7, 10]. These reactions will be discussed in Chapter 9 of this book.

B. Carbonyl-substituted Cyclopropanes

As with the previous section, this one will mainly be confined to synthetic applications of cyclopropane derivatives activated by only *one* carbonyl group.

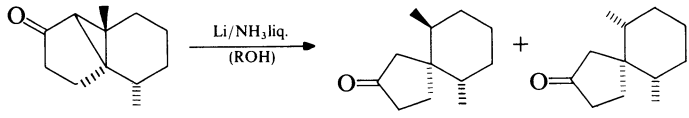
1. Reductive cleavage

Catalytic hydrogenation will usually open the less hindered bond adjacent to the carbonyl-substituted cyclopropane carbon[35]. Therefore, construction of the sinularene skeleton has become possible (cleavage of bond a); on the other hand, Cr(II) breaks the more shielded C–C bond (cleavage of bond b) in a very similar compound yielding the longifolene system (equation 34)[78].



(34)

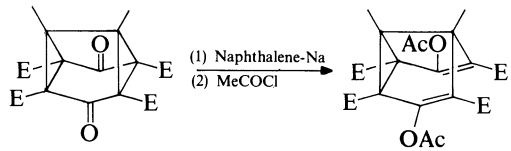
Reductive opening with zinc only occurs with vicinal diactivated cyclopropanes[12, 79], whereas lithium in liquid ammonia also works with compounds having one activating substituent. In this case the bond overlapping most effectively with a C=O group is broken[12, 80]. The degree of stereoselectivity, however, is largely dependent on the proton source present and on the reaction temperature (equation 35)[81] as well as on the nature of more remote substituents[82].



(35)

– 78°C, no alcohol	94 : 6	55%
– 33°C, excess MeOH	57 : 43	60%

In the early seventies Stork and his students[83] have shown that the intermediate enolate can be trapped by suitable electrophiles, e.g. alkyl halides, giving substituted ring-opened products. These modes of cyclopropane opening have been used for the synthesis of several natural compounds[84]. A tetra-activated cyclopropane is cleaved by sodium naphthalene in a preparation of a specifically substituted semibullvalene (equation 36)[85].

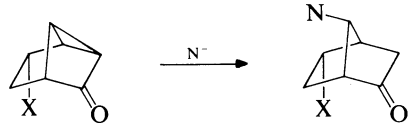


(36)

E = CO_2Me

2. *Ring-opening with carbon- and heteronucleophiles*

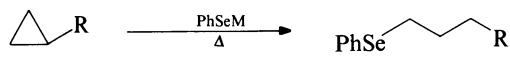
Most frequently, cuprates or other C-nucleophiles are employed in homo-Michael additions which often serve as the basic reactions for constructing natural product skeletons[7, 10]. The preparation of optically active compounds also profits from this type of approach[86]. Usually, monoactivated cyclopropanes are opened by nucleophiles only if they have additional strain. As shown in equation 37, this holds true for tricyclo[3.2.0.$0^{2,7}$]heptan-6-on derivatives, which are easily available from cyclopentadiene and dichloroketene, leading to products serving as prostaglandin precursors[87].



(37)

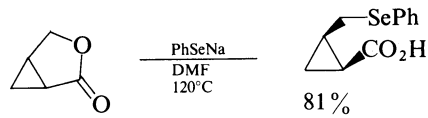
X = OR, Br $N^- = MeO^-, CN^-$, cuprates

Only very powerful soft nucleophiles like phenylselenolate and phenylthiolate ions are capable of opening monoactivated cyclopropanes (equation 38), whereas formation of a cyclopropane carboxylate has been observed with the bicyclic lactone in equation 39[88].



(38)

R = COMe, CN M = Li, Na 90%, 47%

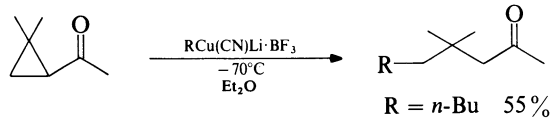


(39)

81%

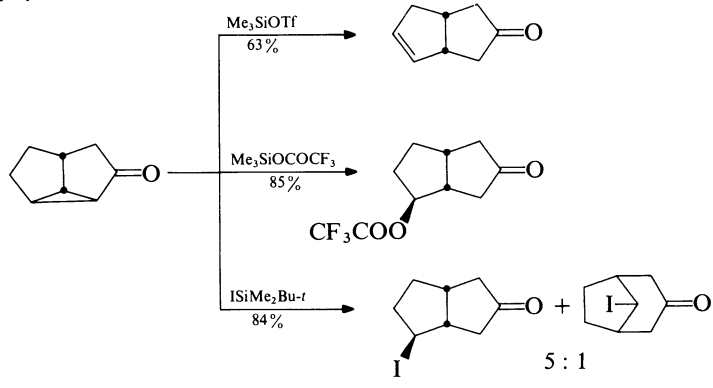
3. *Ring-opening triggered by electrophiles*

Acceptor ability of a group can be enhanced by interaction with a suitable electrophile (proton, Lewis acid). This is very likely in the $Ni(acac)_2$-catalysed reaction of cyclopropyl ketones with trimethylaluminium[89] and in the synthetically more significant addition of several cuprates to alkyl cyclopropyl ketones. The BF_3-activated organometallic reagent attacks the less substituted cyclopropane carbon regioselectively. Yet steric hindrance can be a problem in this reaction (equation 40)[90].

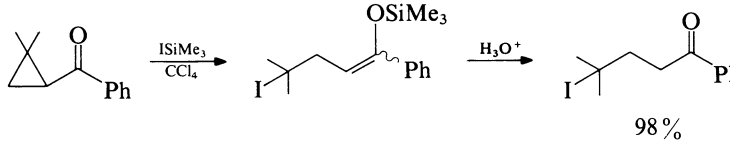


R = *n*-Bu 55%
R = *s*-Bu 35%
R = *t*-Bu 0% (40)

Homoconjugate additions of secondary amines to cyclopropyl ketones catalysed by acid have been reported[91] as well as formation of certain 5,6-dihydro-4*H*-1,2-oxazines with hydroxylamine hydrochloride[92]. Demuth and Mikhail have recently demonstrated that cyclopropanes of the tricyclo[3.3.0.$0^{2,8}$] octan-3-one type can be selectively converted to functionalized bicyclic compounds with different kinds of electrophilic/nucleophilic reagents (equation 41)[93]; the products have extensively been exploited for natural product synthesis[94].

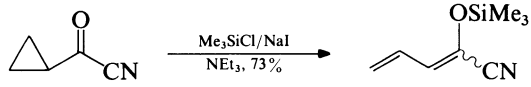


(41)



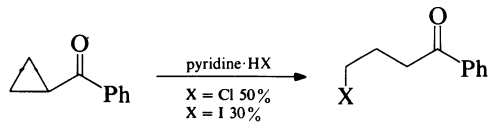
(42)

By action of trimethylsilyl iodide, simple cyclopropyl ketones are transformed into silyl enol ethers which are generally hydrolysed to the corresponding γ-iodoketones (equation 42)[95]. Interestingly, the more substituted cyclopropane carbon is attacked by the iodide. A related reaction occurs with the combination Me_3SiCl/metal-X which introduces the nucleophile X^- to the opened product[96]. This approach leads to synthesis of several γ-butyrolactones[97]. Similarly, cleavage of an acyl cyanide with Me_3SiCl/NaI has been observed; addition of base results in the formation of an interesting bifunctional diene[98] (equation 43). One-pot preparation of a γ-chloroketal by action of ethylene glycol on a cyclopropyl ketone in the presence of $SiCl_4$ has also been performed[99].

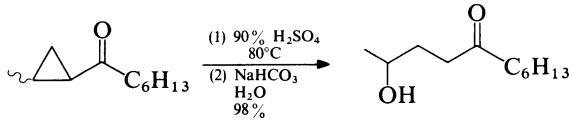


(43)

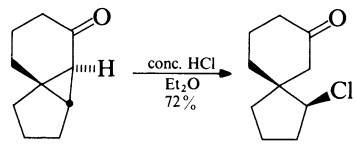
Very often protic acids are used to cleave electrophilic cyclopropanes. Some typical examples are given in equations 44–46[84b, 100–102].



(44)

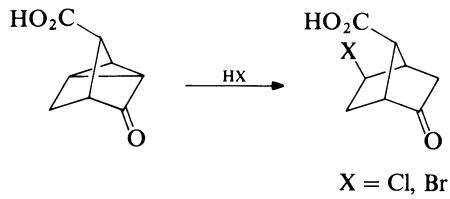


(45)



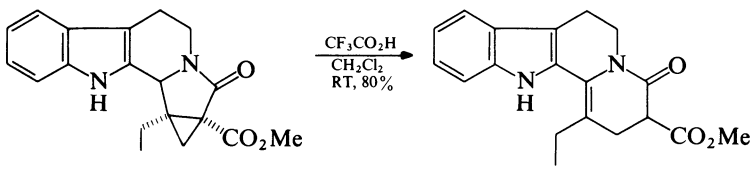
(46)

The cyclopropyl ketone displayed in equation 47—accessible from norbornadiene and formaldehyde via the Prins reaction—can serve as a versatile starting material for the synthesis of prostaglandins[103], pseudoguainolides[104] and steroids[105]. Stereochemical aspects of HBr addition to cyclopropyl ketones have been studied[106].



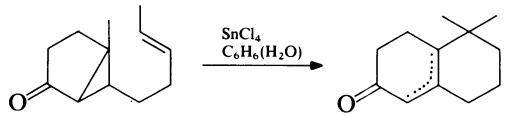
(47)

In this kind of cyclopropane ring-opening olefins are currently generated by elimination. An approach to spiro-vetivones[107, 108] and a synthesis of indole alkaloids (equation 48)[109] take advantage of this property.



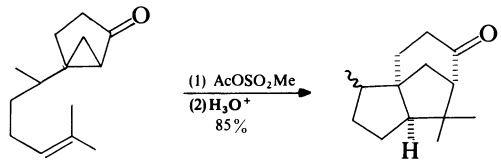
(48)

In many cases the nucleophile involved in (Lewis) acid-promoted cyclopropane ring-opening is a π-system, which can be attacked intra- and intermolecularly. Early examples were given by Stork and coworkers who also showed that alkyl group shifts can follow the C–C bond-forming step[110] (equation 49). Syntheses of cedrone and a cholchicin derivative made use of this acid-induced ring-opening/cyclization sequence (equations 50 and 51)[111, 112].



(49)

(two olefinic isomers)



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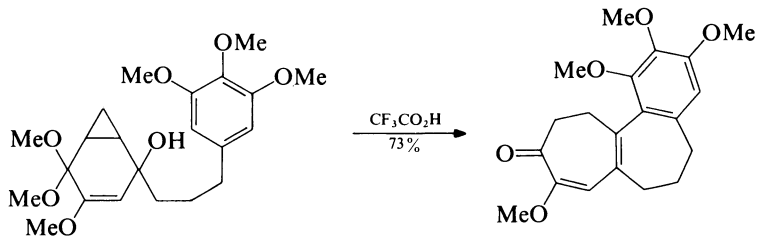
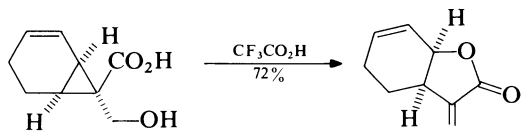


(51)

Certain tetralones which result from aryl aroylcyclopropanes by tin tetrachloride action[113] were utilized in a synthesis of picropodophyllone[113b]. Similarly, indanones are available from cyclopropyl phenyl ketone[114a], whereas reaction of ethyl cyclopropanecarboxylate in benzene or toluene under Friedel-Crafts conditions gives the same class of compounds in an intermolecular fashion[114b].

Further activation and functionality is introduced to cyclopropyl ketones or esters by an additional hydroxymethyl substituent or its equivalent. On this basis, a synthesis of α-methylene γ-butyrolactones has been performed (equation 52)[115].

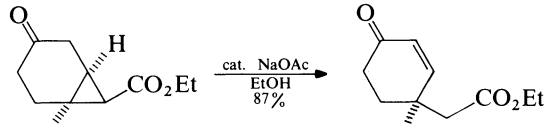


(52)

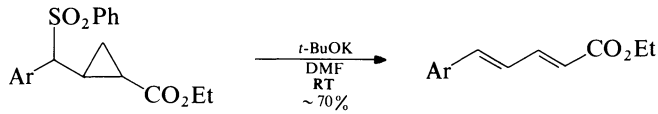
4. Ring-opening assisted by C-donor substituents

A donor group located vicinally is another means for rendering acid or base-induced ring cleavage easier. Deprotonation of a suitably activated side chain can induce this donor property of a substituent as shown in equations 53 and 54. The first example leads to a precursor for a trichodermin synthesis[116]; in analogy, a brefeldin A precursor has been

prepared[117], and α-patchoulen, α-cedren and hinesol syntheses[118] involve this type of ring-opening.

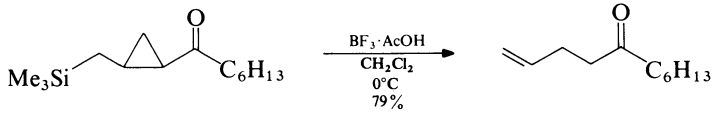


(53)

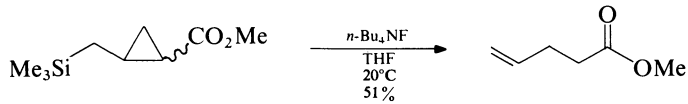


(54)

Equation 54 describes the preparation of dienes by a similar cyclopropane cleavage followed by proton transfer and elimination of sulfinate[119]. The weak donor ability of a (trimethylsilyl)methyl group also assists Lewis acid-promoted ring cleavage according to equation 55, which allows synthesis of γ, δ-unsaturated ketones[120]. Interestingly, the related ester opens smoothly only if fluoride reagents are employed (equation 56)[121].



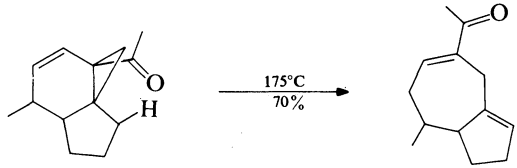
(55)



(56)

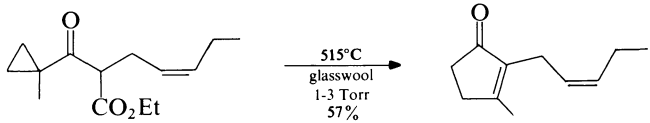
5. *Thermal ring-openings*

Thermal openings of cyclopropyl ketones involve homo[1,5]-hydrogen shift, which can serve as a prerequisite for ring enlargement (equation 57)[122]. 2,3-Disubstituted cyclopentanones have also been made by using this rearrangement[123].



(57)

A unique thermal cleavage of certain cyclopropyl ketoesters has been reported by Berkowitz[124]. The intermediacy of a ketene and its rearrangement together with carbon monoxide loss is postulated. This sequence has led on to the preparation of *cis*-jasmone (equation 58)[124b].



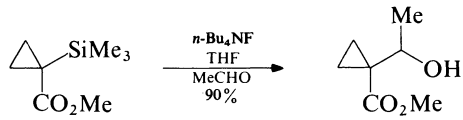
(58)

1,1-Diacetylcyclopropane expands to 2-methyl-3-acetyl-4,5-dihydrofuran at 200°C[125]. This rearrangement has also been recorded at 190°C with a related, more substituted compound, which, however, at higher temperatures yields a naphthalene derivative[126].

VI. HETEROSUBSTITUTED CYCLOPROPANES

A. Silicon as Heteroatom

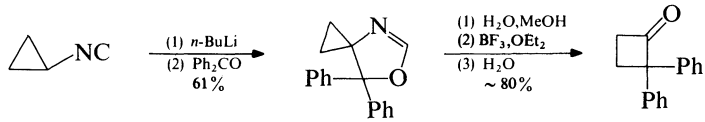
An excellent review by Paquette[15], who developed much of the silylcyclopropane chemistry, gives a first insight into this field. Strong electrophiles cleave silyl-substituted cyclopropanes, but regioselectivity problems diminish the synthetic practicability[127, 128]. A new method to prepare 1-hydroxyalkylated cyclopropanecarboxylates involves desilylation-aldol-addition of a methyl silylcyclopropanecarboxylate (equation 59)[129]. Products obtained via this smart route might be of interest for further transformations. Additional examples of silylcyclopropane chemistry will be described in Section VII dealing with vinylcyclopropanes.



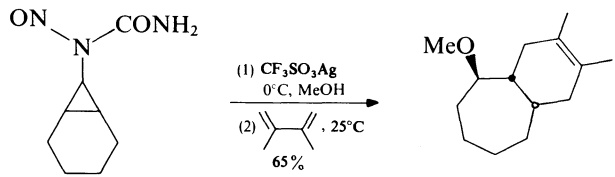
(59)

B. Nitrogen and Phosphorus as Heteroatoms

Reactions of aminocyclopropanes are discussed extensively in Chapter 22 of this book, therefore only some 'unusual' aminocyclopropanes will be treated here. One example is cyclopropyl isocyanide which after deprotonation, reaction with carbonyl compounds, and hydrolysis can be transformed to cyclobutanones (equation 60)[130], thereby taking advantage of the acidifying effect of the isocyanide function. 7-Norcarane nitrosourea is the key starting material in Jendralla and Spur's approach to *trans*-cycloheptene adducts (equation 61)[131].

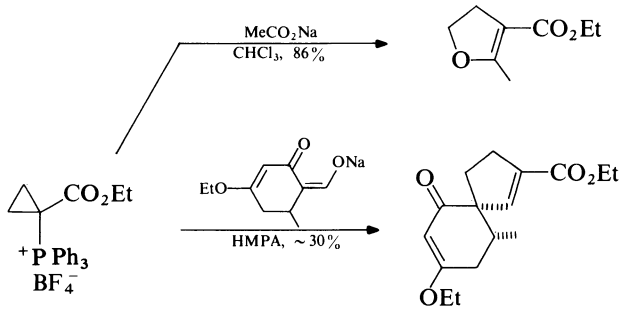


(60)

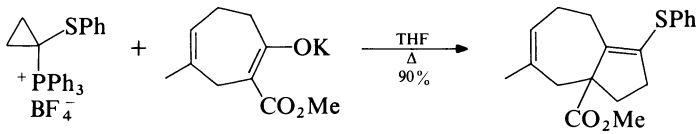


(61)

Schweitzer has synthesized alkylidene cyclopropanes by Wittig reaction with a cyclopropyl phosphonium salt[132]. If, however, the electrophilic character of the cyclopropane is enhanced by a second acceptor group (e.g. CO_2R, SR), suitable nucleophiles are able to attack the three-membered ring. The resulting ylid can form hetero- and carbocycles by an intramolecular Wittig reaction[133–138] as demonstrated in equations 62 and 63. These annulation reactions have been applied to terpene and alkaloid preparations.



(62)



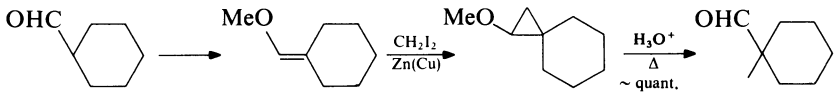
(63)

C. Oxygen as Heteroatom

Although many reviews deal with certain aspects of oxycyclopropanes[4-6, 13, 14, 16, 18-20, 139], there is no general treatment of this class of cyclopropanes. Oxycyclopropanes can be regarded as masked carbonyl compounds and for this reason display a particularly rich and very practicable chemistry.

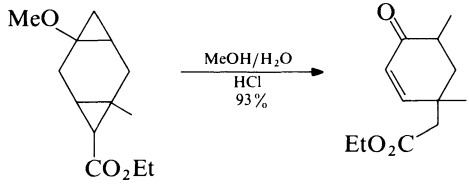
1. Oxycyclopropanes with no further functional group at the three-membered ring

Alkoxycyclopropanes are commonly prepared from alkyl enol ethers by one of the Simmons–Smith modifications (see Chapter 7). According to Wenkert and coworkers they are cleaved by strong acids to the α-methylated carbonyl compound, thus establishing an overall α-methylation of a ketone or an aldehyde[140] (equation 64). This method has often been used for natural product synthesis (e.g. valerane[141]).



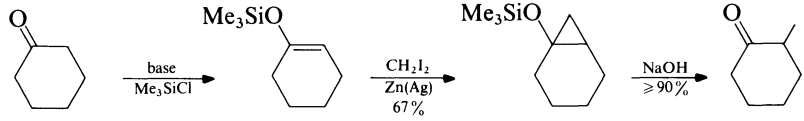
(64)

During preparation of 9-pupukeanone a related acid-induced double fragmentation of a tricyclic compound has been applied (equation 65)[142]. When treated with base, cyclopropanols and the more easily available siloxycyclopropanes open to the corresponding

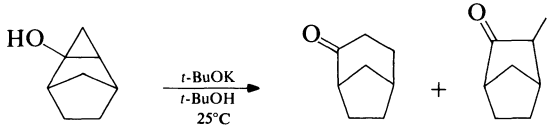


(65)

carbonyl compounds. This also constitutes an α-methylation (equation 66), a method studied extensively by Conia[5, 143] and others[144]. The cyclopropane is mostly opened in a direction which generates the more stable 'carbanion' (the primary one in the majority of cases). However, exceptions are known, for instance in polycyclic systems (equation 67)[145], where ring expansions have been observed. This constitutes one of the key steps for a synthesis of hirsutene[146].



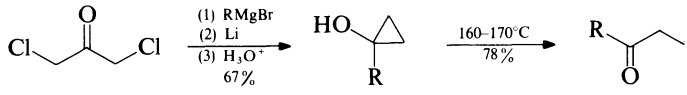
(66)



(67)

90:10

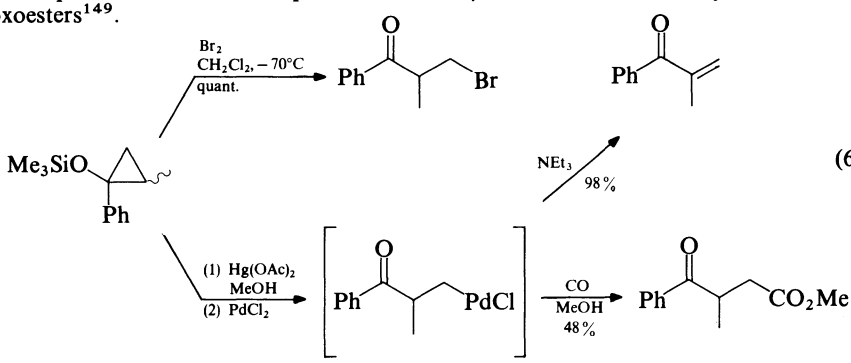
An interesting variation has recently been described using 1,3-dichloroacetone for the preparation of alkyl ketones via cyclopropanol intermediates (equation 68)[147].



(68)

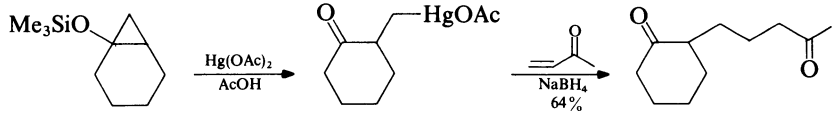
R = 

Although it has been well known that cyclopropanols are cleaved by apt electrophiles[4], this process was only applied for synthetic purposes when good methods for the preparation of siloxycyclopropanes had been worked out. Murai and coworkers' investigations[18] demonstrate that transformations according to equation 69 using strong electrophiles lead to versatile products such as β-bromoketones[148], vinyl ketones or γ-oxoesters[149].



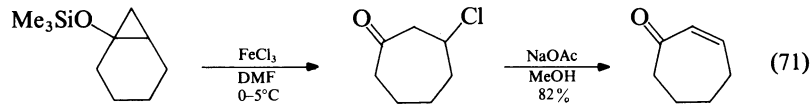
(69)

A carbonylation reaction with $Ni(CO)_4$ generating 1,4,7-tricarbonyl compounds has also been published[150]. Synthesis of 1,6-dicarbonyl systems via mercury(II) intermediates and radical chain additions to electrophilic olefins has been achieved (equation 70). This sequence constitutes an umpolung if one considers that the carbonyl moiety is masked in siloxycyclopropanes[151]. *Threo*-juvabione has been synthesized from a methoxycyclopropane via a mercury(II) salt cleavage/reduction sequence[152].

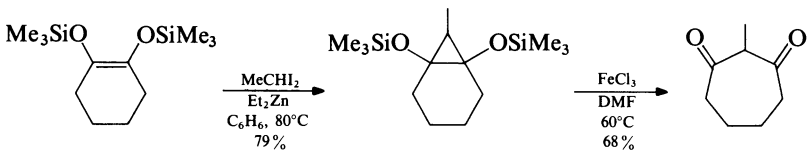


(70)

Oxidative ring-openings of different oxycyclopropanes have been reported, but their synthetic value is restricted to few examples[153, 154]. As found by Saegusa and coworkers, siloxycyclopropanes undergo ring-opening with $FeCl_3$ in dimethylformamide forming β-chloroketones which can be transformed to α,β-unsaturated compounds (equation 71)[155]. 1,2-Bis-siloxycyclopropanes provide 1,3-dicarbonyl compounds directly (equation 72)[156, 157].

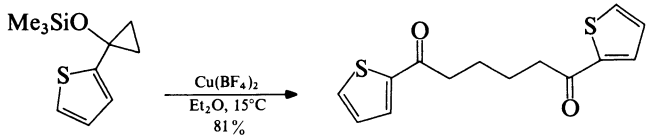


(71)



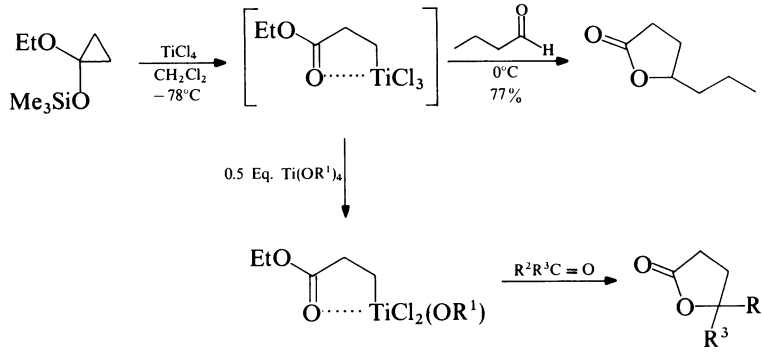
(72)

Contrary to the common electrophilic attack at the least substituted cyclopropane carbon, the higher substituted C–C bond is cleaved under these oxidative conditions. Reaction of siloxycyclopropanes with silver(I) or copper(II) tetrafluoroborate leads to 1,6-diketones (equation 73)[158]. Here, electrophilic opening and oxidative dimerization must be assumed.



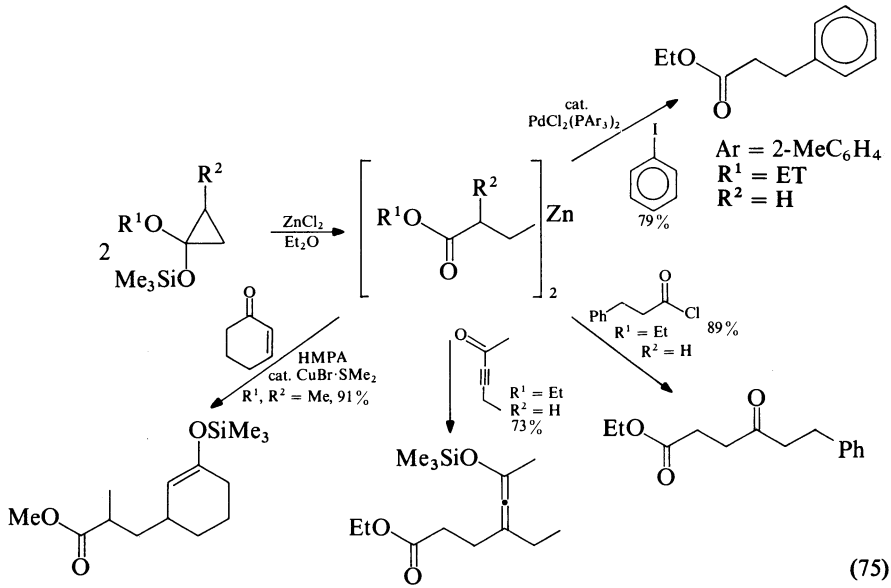
(73)

Geminal bis-oxygenated cyclopropanes (i.e. cyclopropanone acetals) are more activated towards the attack of electrophiles. This is why the Kuwajima group could take advantage of 1-ethoxy-1-trimethylsiloxycyclopropane as a homoenolate equivalent. Reaction of this compound with aldehydes under $TiCl_4$ promotion gives γ-butyrolactones in high yield (equation 74)[159]. The intermediate titanium homoenolate can be isolated, characterized and reacted with bromine or oxygen providing β-bromo- or β-hydroxyesters[160].



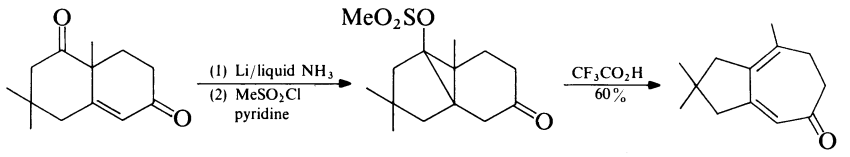
(74)

Although acetals give γ-alkoxyesters, ketones do not react with trichlorotitanium homoenolates. Only by replacing one of the chlorine atoms by an alkoxy ligand is a more nucleophilic species generated which is capable of smooth addition to ketones (equation 74) and sterically hindered aldehydes[161]. As a further point, zinc homoenolates can also be prepared by reaction of zinc chloride with this siloxycyclopropane. These reagents add to α,β-unsaturated ketones and to electrophilic acetylenes in a conjugate fashion if hexamethyl phosphortriamide (HMPA) and a catalytic amount of $CuBr \cdot SMe_2$ are present (equation 75). Trimethylsilyl chloride, formed in the first step, is essential for the addition reactions, which allow syntheses of promising functionalized compounds. Acid chlorides as electrophiles lead to γ-oxoesters. Addition of a palladium catalyst to the zinc species allows arylation and vinylation of the homoenolate in good yield[162].



(75)

The ability of a methanesulphonate substituent to function as a leaving group (compare equation 124, Section VI.E.2) in an intermediate cyclopropane permits transformation of a bicyclo[4.4,0]decene derivative into a compound with a hexahydroazulene skeleton having potential for sesquiterpene synthesis[163] (equation 76).



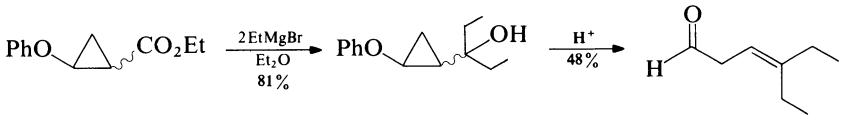
(76)

2. *Oxycyclopropanes with additional activating substituents*

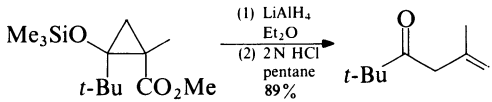
Further activating substituents (acceptor or leaving groups) allow ring-opening of oxycyclopropanes under different, usually milder conditions. In addition, new modes of cyclopropane cleavages are possible.

a. α-Hydroxymethyl derivatives.

Due to the higher oxidation level cyclopropylcarbinyl–homoallyl rearrangement (see also Section IV.C) of oxycyclopropanes gives β,γ-unsaturated carbonyl compounds. This feature has been discovered by Julia and coworkers, who reacted certain esters with Grignard reagents or $LiAlH_4$. The corresponding cyclopropyl carbinol opens under acidic conditions to β,γ-unsaturated aldehydes (equation 77)[164]. This conversion also works for other types of oxycyclopropanes[165, 166] as shown in equation 78[167].

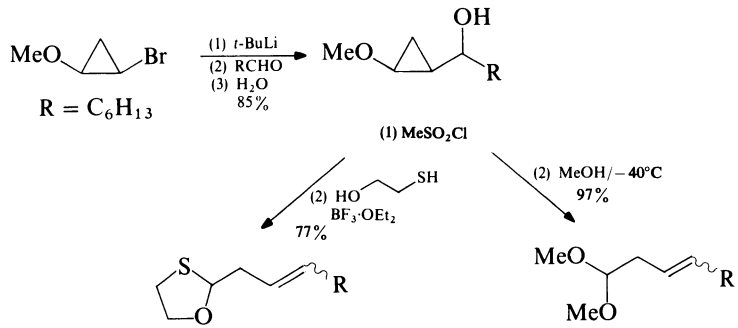


(77)



(78)

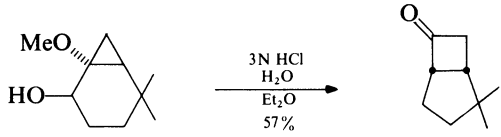
Another strategy for assembling the carbon skeleton has been developed by Corey and Ulrich[168] using 2-methoxycyclopropyllithium, generated from the corresponding bromoethers (equation 79). The aldehyde can be liberated from the hemithioacetals under mild conditions.



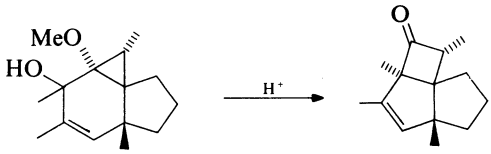
(79)

E:Z = 83:17

If the hydroxyalkyl function and the oxy substituent are linked to the same cyclopropane carbon, the pattern is perfect for a cyclopropylcarbinyl–cyclobutanone rearrangement. This allows a very convenient access to cyclobutanones (equation 80)[140,169–172]. The method was used in syntheses of grandisol[141], poitediol[173] and isocomene (equation 81)[174].

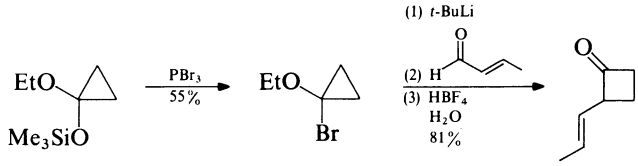


(80)



(81)

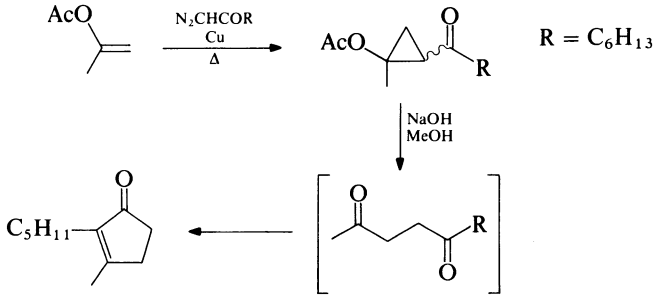
A new effective route employing 1-ethoxy-1-siloxycyclopropane as starting material has been reported (equation 82)[175].



(82)

b. Carbonyl-substituted oxycyclopropanes.

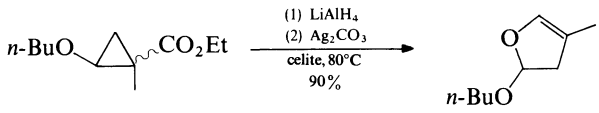
Although it has been known since 1938 that alkoxy-substituted alkyl cyclopropanecarboxylates can be opened to 1,4-dicarbonyl compounds[176] it was not until 1970 that the synthetic merit of this route to a valuable class of intermediates was recognized. In this year Wenkert and coworkers described the preparation of cyclopentenones from this type of cyclopropane via 1,4-diketones as outlined in equation 83[140]. Shortly later McMurry and Glass have published a *cis*-jasmone synthesis following the same principle[177].



(83)

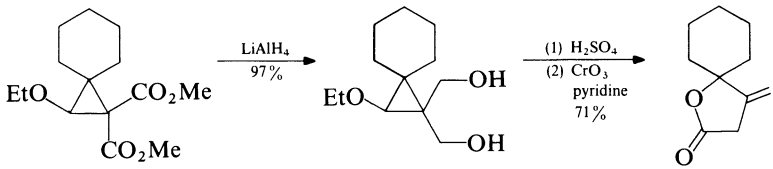
Similarly, 2-methoxy cyclopropylketones form γ-ketoaldehydes[178] and ethyl alkoxycyclopropanecarboxylates lead to γ-oxoesters after treatment with strong acid[140,179]; the corresponding cyclopropanecarboxylic acids afford γ-oxoacids by heating in

water/methanol[180]. In many syntheses of natural products or their precursors advantage has been taken of the easy availability of 1,4-dicarbonyl compounds via this route[181-184]. A modified reduction/oxidation sequence gives alkoxy dihydrofuranos (equation 84)[185, 186].



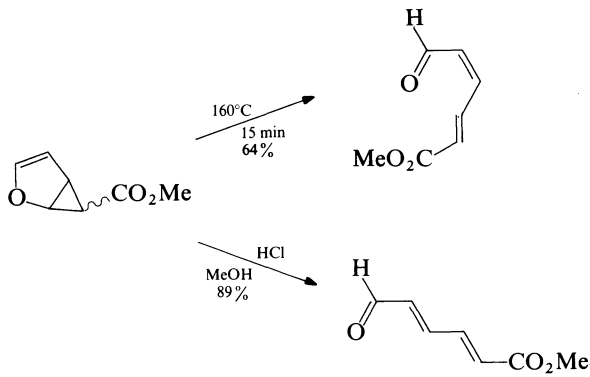
(84)

Use of ethyl diazopyruvate or 1-diazo-3,3-dimethoxy-2-butanone for cyclopropanation introduces additional functionality into the ring-opened products[186, 187]. β-Methylene γ-butyrolactones result from bisalkoxycarbonyl-substituted cyclopropanes in three steps (equation 85)[185].



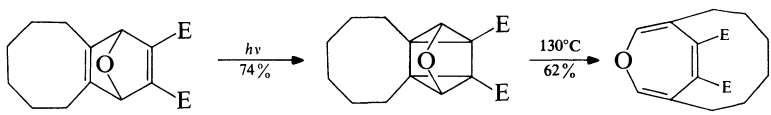
(85)

Cyclopropanation of 1-oxy-1,3-dienes is not regioselective[188]. However, certain homofuran derivatives can yield highly electrophilic dienes as demonstrated in equation 86[189]. This reaction has served as one of the basic steps in a synthesis of the arachidonic acid metabolite 5-HETE (5-hydroxyeicosatetraenoic acid)[190].



(86)

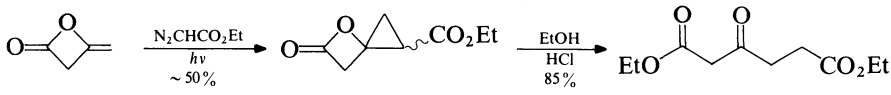
A donor–acceptor substituted biscyclopropane is an intermediate in an elegant preparation of a β,β'-bridged hexano-oxepin, which is formed by an electrocyclic ring-opening (equation 87)[191].



(87)

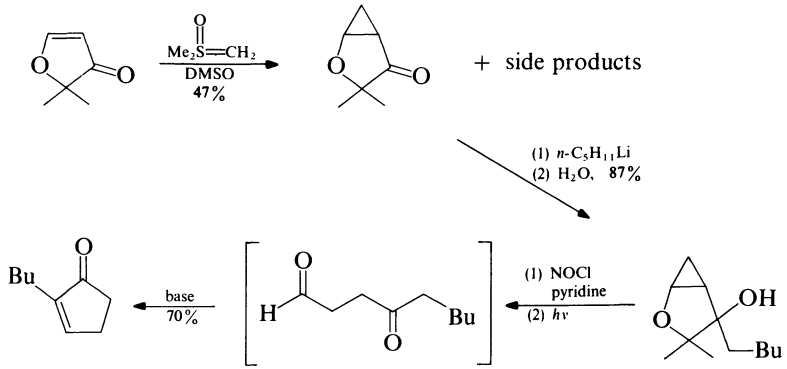
E = CO_2Et

Several other examples of acceptor-activated oxycyclopropanes have been described. However, useful transformations are rare. Exceptions are Kato's diketene adducts which provide interesting tricarbonyl compounds after acid or base treatment (equation 88)[192]. Unfortunately, the yields in the cyclopropanation step are frequently only moderate.



(88)

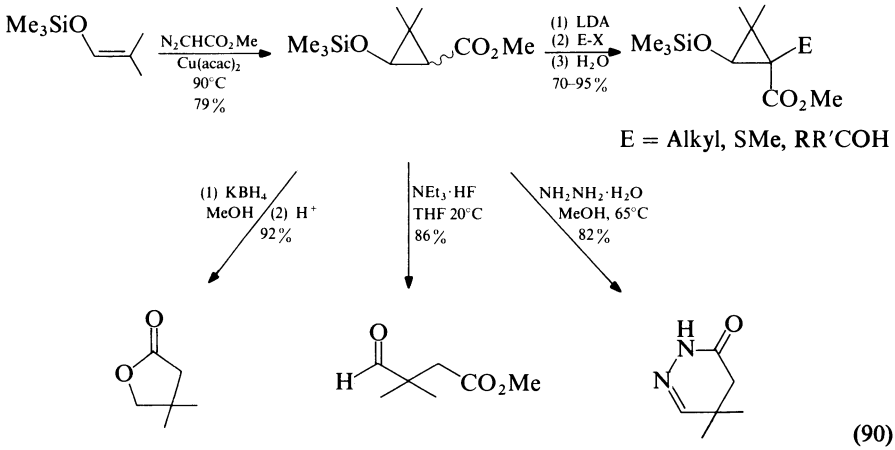
The same disadvantage presents itself in the synthesis of bicyclic donor acceptor cyclopropanes (equation 89), which result in cyclopentenones after Barton fragmentation and aldol condensation[193].



(89)

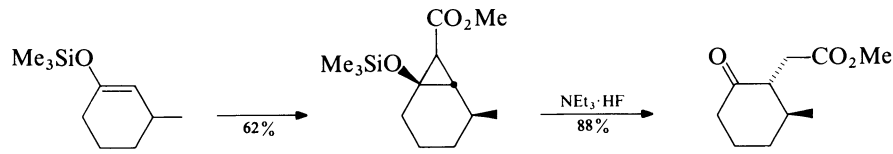
Despite many practicable synthetic applications of alkoxycyclopropanes described so far there are severe drawbacks in their reactions. First, methods for preparation of the corresponding alkoxyalkenes are sometimes tedious and usually poor as far as chemo-, regio- and stereoselectivity are concerned. Second, the efficiency of the cyclopropanation step is often rather low, probably due to purification problems. Third, the conditions for cleavage of alkoxycyclopropanes are relatively harsh (strong acid or base) and are not compatible with many functional groups.

Not surprisingly, shortly after their synthetic power has been recognized silyl enol ethers have been used as substrates for electrophilic carben(oid)s. Although mainly ring-opened products have been isolated in the first attempts[194, 195], preparation of methyl 2-siloxycyclopropanecarboxylates proceeds in very good yields (equation 90)[196] even in large-scale reactions. The regio- and stereochemistry is completely transferred to the cyclopropanes. These can be further substituted at C(1) with E in a very flexible manner applying an effective and stereoselective[197] deprotonation/alkylation sequence—the first examples having been effected for alkyl cyclopropanecarboxylates[198].

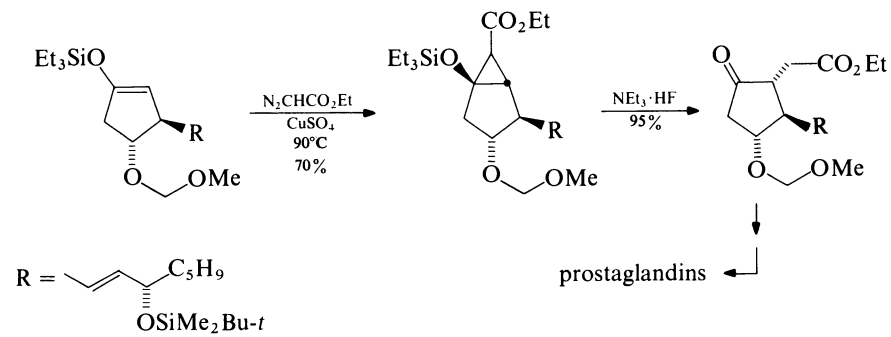


(90)

Although these cyclopropane derivatives are distillable and stable to a variety of reagents, they can be cleaved under extremely mild conditions due to the presence of the R_3SiO group. Thus, fluoride sources like $NEt_3 \cdot xHF$ ($x = 1$–3)[199], *n*-Bu_4NF or $PhCH_2Me_3NF$ generate γ-oxoesters in excellent yields[196a,200]. This method is of particular importance for the preparation of formyl esters, which are not efficiently obtainable by other routes (equation 90), and of oxoesters with defined stereochemistry and labile functional groups. As demonstrated in equation 91, the *trans* relationship built up in the cyclopropanation step is preserved during the mild ring cleavage[200]; a prostaglandin synthesis (equation 92)[201] profits from this quality and reflects efficiency and high chemo- and regioselectivity of this approach.



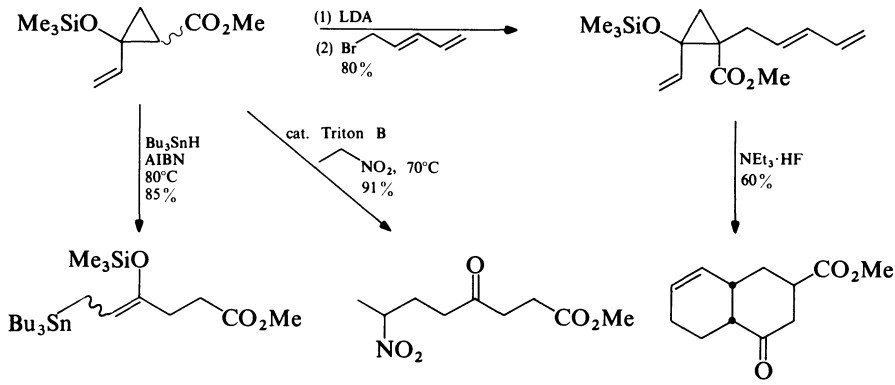
(91)



(92)

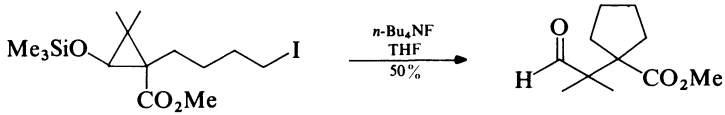
Short-cut one-pot procedures to various 1,4-dioxo systems[200, 202, 203] and to heterocycles like γ-butyrolactones[204] or pyridazine derivatives[205] make use of methyl 2-siloxycyclopropanecarboxylates as masked 1,4-dicarbonyl compounds (equation 90). Transformation to very sensitive β,γ-unsaturated carbonyl systems has been mentioned earlier (equation 78)[167].

Compounds with an additional 2-vinyl group, easily available in two steps from α,β-unsaturated ketones, are of special interest. If the reactive vinyl ketone moiety is liberated, it can be trapped *in situ* by suitable nucleophiles, e.g. CH-acids, generating polyfunctional compounds[206] or by a diene unit which undergoes an intramolecular Diels–Alder reaction[203] (equation 93). Besides, radical additions to the vinylcyclopropane are also possible giving silyl enol ethers as ring-opened products[203]. Future synthetic applications of theses processes are obvious.

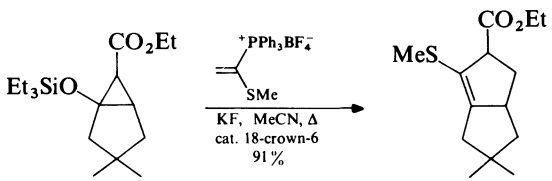


(93)

With fluoride ion under aprotic conditions alkylating ring-opening can be performed[200] (equation 94). Similarly, a clever [3 + 2] annulation combines a fluoride-induced Michael addition to vinyl phosphonium salts with a subsequent internal Wittig reaction (equation 95)[207].



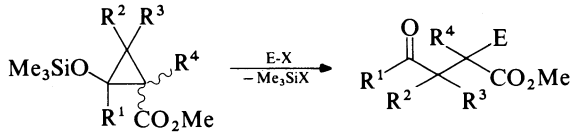
(94)



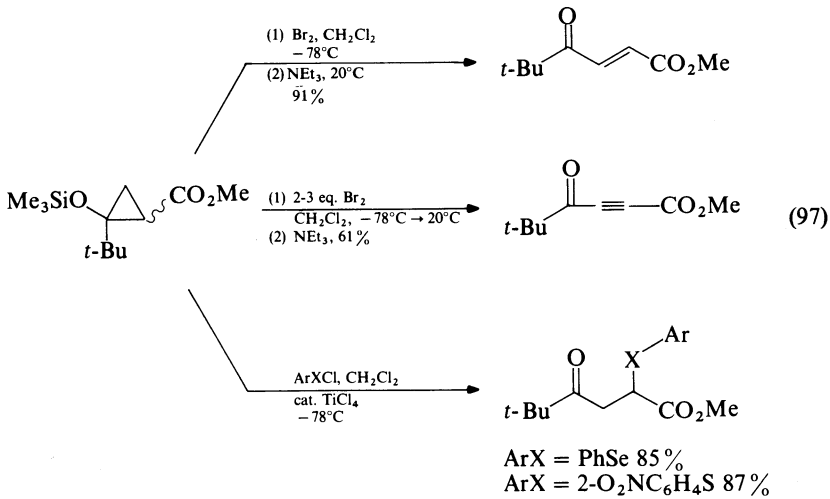
(95)

Methyl 2-siloxycyclopropanecarboxylates are opened by strong electrophiles E-X with formation of α-substituted γ-oxoesters or their products (equation 96). In all examples examined the regioselectivity of the process is strongly controlled by the ester function causing cleavage of the bond between donor and acceptor group. This behaviour could be

utilized for an easy synthesis of electrophilic olefins and acetylenes by reaction with bromine followed by dehydrobromination (equation 97)[208].



(96)



(97)

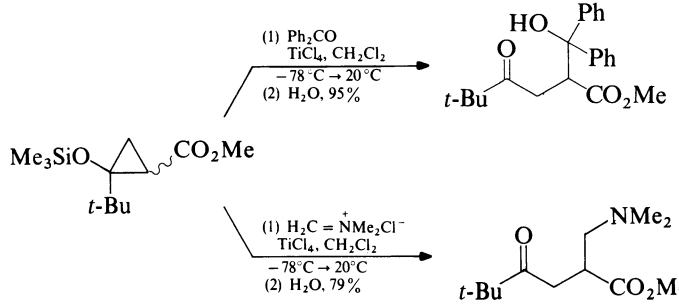
ArX = PhSe 85%
ArX = 2-$O_2NC_6H_4S$ 87%

Selenenylation occurs in a similar manner. However, this process is much faster and cleaner if performed in the presence of a catalytic amount of $TiCl_4$ at $-78°C$. The catalysis by Lewis acid is essential for the related sulphenylation[209]. A mechanistic rationalization, which is in accordance with a Lewis acid-catalysed *cis–trans* isomerization at low temperature[210], is depicted in equation 98.

(98)

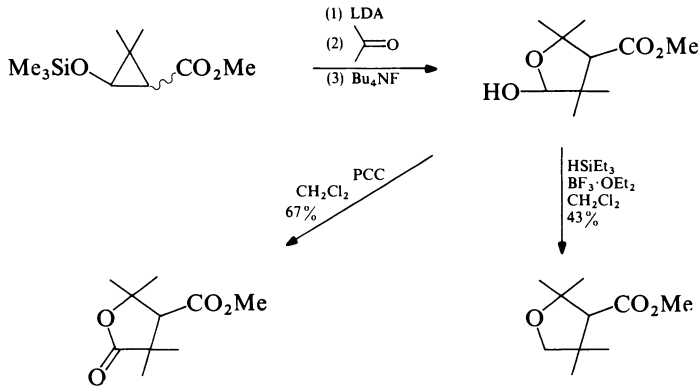
LA = Lewis acid

The ring-opened dipolar intermediate suggests reactivity towards nucleophiles and electrophiles. The latter occurs in the $TiCl_4$ promoted addition of methyl 2-siloxycyclopropanecarboxylates to carbonyl compounds[211] and to an iminium salt[209] (equation 99). The products of both processes are very versatile intermediates allowing synthesis of different furan derivatives and other compounds[209,211]. Concerning the liberated carbonyl function, both reactions can be classified as homoenolate additions, thus putting further emphasis on the cyclopropane homoalkene equivalence.



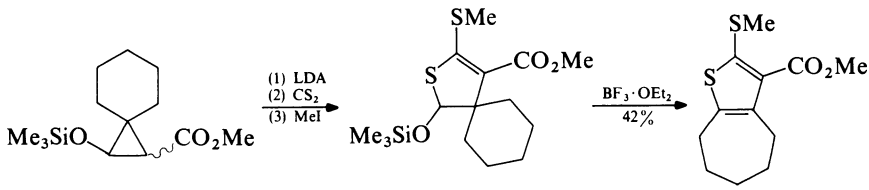
(99)

A complementary entry to hydroxyalkylated products has been opened by deprotonation, carbonyl compound addition and ring-opening as outlined in equation 100[203]. The resulting γ-lactols are precursors to γ-butyrolactones or tetrahydrofuran derivatives.



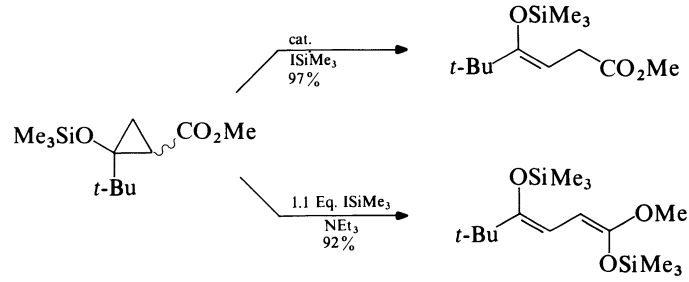
(100)

The ester enolates and their additions to CS_2 or PhNCS also provide a surprising possibility of thiophene and pyrrole synthesis via novel ring enlargements (equation 101)[203,212]. Aromatization happens on treatment with acids either by elimination of Me_3SiOH or by a Wagner–Meerwein alkyl shift.



(101)

Little quantities of iodotrimethylsilane catalyse the rearrangement of 2-siloxy cyclopropanes to their isomeric silyl enol ethers (equation 102), whereas an equimolar amount of this silylating agent gives a highly donor substituted diene[213]. Both product types are promising intermediates, yet their chemistry still remains to be explored.



(102)

Another approach to acceptor-substituted siloxycyclopropanes has recently been described[214]. Here, a 1,3-dicarbonyl compound is converted to the corresponding β-trimethylsiloxy α,β-unsaturated ketone or ester. Cyclopropanation and ring-opening gives 1,4-dicarbonyl compounds, however, conversions and yields are moderate.

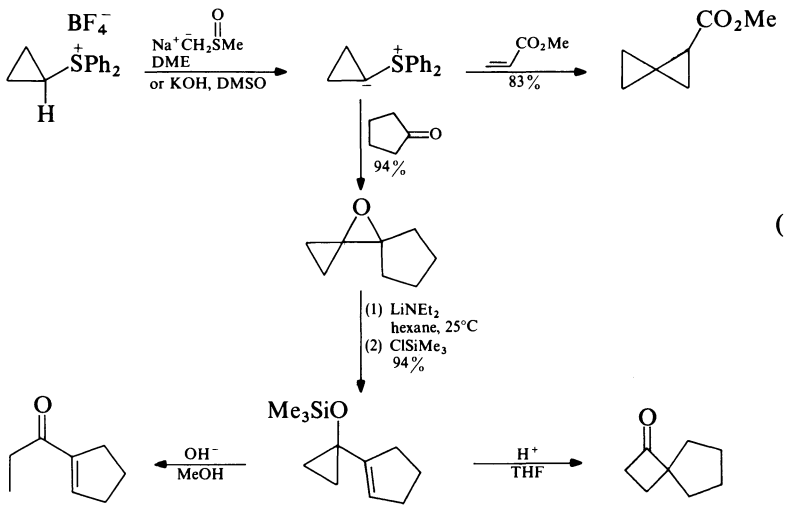
Summing up, siloxy cyclopropanecarboxylates are building blocks of extreme versatility, and many novel applications and new reactions may be expected within the nearest future.

D. Sulphur- and Selenium as Heteroatoms

1. Aryl- and alkylthio-substituents

α-Aryl- and alkylthio-substituents stabilize positive and negative charges; this is why they can serve both as donor *and* as acceptor groups. Owing to this dichotomy the chemistry of sulphur-substituted cyclopropanes is especially manifold.

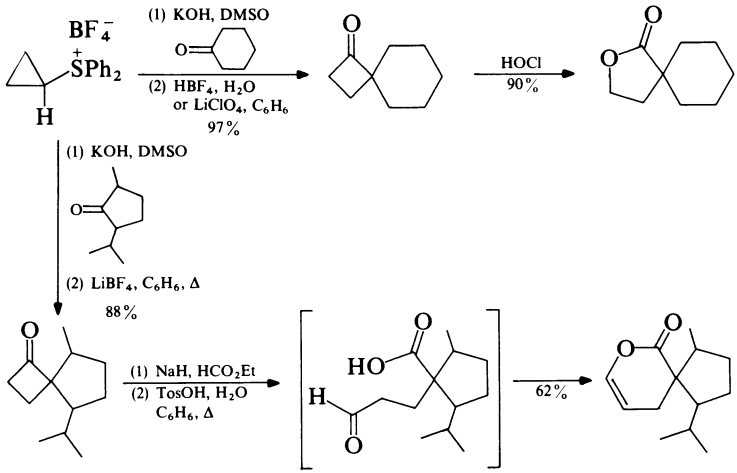
A lot of progress in this area is due to the work of Trost[3], who introduced diphenylsulphonium cyclopropylide and phenylthiocyclopropyl lithium as extremely versatile C_3-building blocks. The first reagent is easily available from the corresponding sulphonium salt by deprotonation with suitable bases (either under irreversible conditions with dimsyl sodium, or, preferably, in a reversible manner by employing potassium hydroxide in DMSO)[215]. The ylide adds to α,β-unsaturated carbonyl compounds forming



(103)

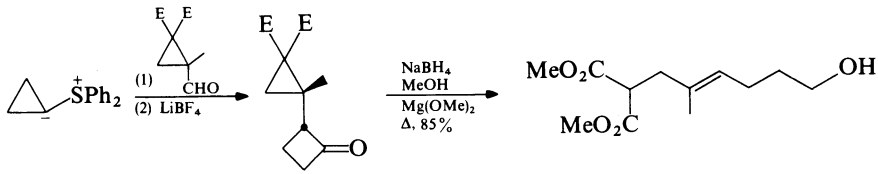
spiropentanes[216] and more importantly, to aldehydes and ketones providing oxaspiropentanes (equation 103)[217].

These epoxides can be converted to vinyl siloxycyclopropanes in high yield by treatment with base and trimethylsilyl chloride. Transformations of these interesting intermediates (see Section VII) into various products are demonstrated in equation 103[217]. Isolation of oxaspiropentanes is not required in a route to cyclobutanones which are formed by straightforward acid workup (equation 104)[218]. These can either be expanded to γ-butyrolactones by oxidation[218] or to an enol ester by α-formylation and acid-induced fragmentation. The latter sequence has been utilized in a synthesis of acorenone B[219].



(104)

An intriguing combination of two cyclopropyl systems allows cyclobutanone formation according to equation 105; base-induced fragmentation of an intermediate cyclobutanol stereoselectively forms a functionalized olefin[220].



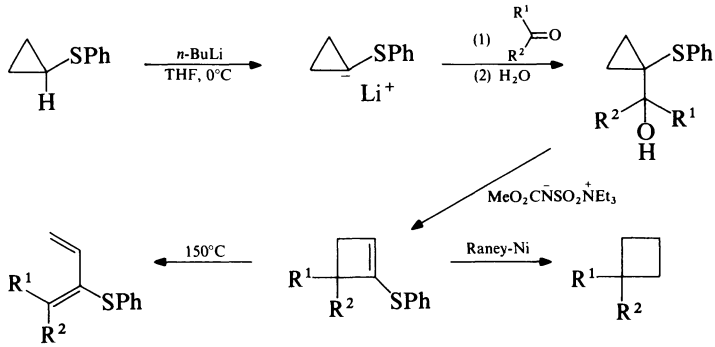
E = CO_2Bu-*t* (105)

In some of the reactions described in equations 103 and 104 the corresponding 2-methyl cyclopropylide has also been used, which provides methyl-substituted products. However, there are certain limitations encountered with the ylide approach:

(*a*) Silver salts are required for the preparation of the sulphonium salt.
(*b*) Sluggish reaction is observed with sterically hindered ketones.
(*c*) Addition to α,β-unsaturated carbonyl compounds occurs in conjugate fashion (equation 103).

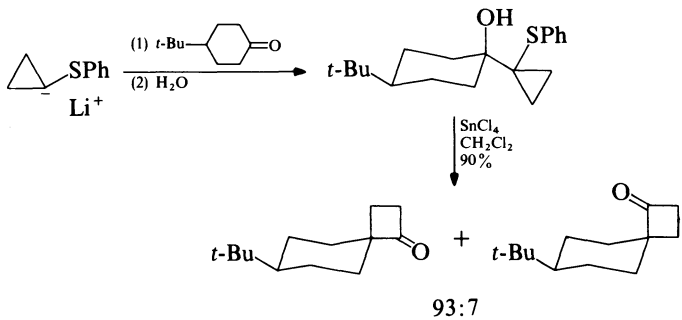
Some of these restrictions can be overcome by use of the more powerful nucleophile phenylthiocyclopropyl lithium available by metalation with *n*-butyllithium as illustrated in equation 106[221]. Although this anion adds cleanly and in excellent yields to most saturated

and unsaturated carbonyl compounds, enolization of hindered ketones is sometimes a cause of trouble. The corresponding 2-methylcyclopropyl phenyl sulphide is metalated to an extent of approximately 70% only and additions to carbonyl compounds render low yields. Therefore this approach is confined to the unsubstituted parent compound, which, however, exhibits an extremely rich chemistry.



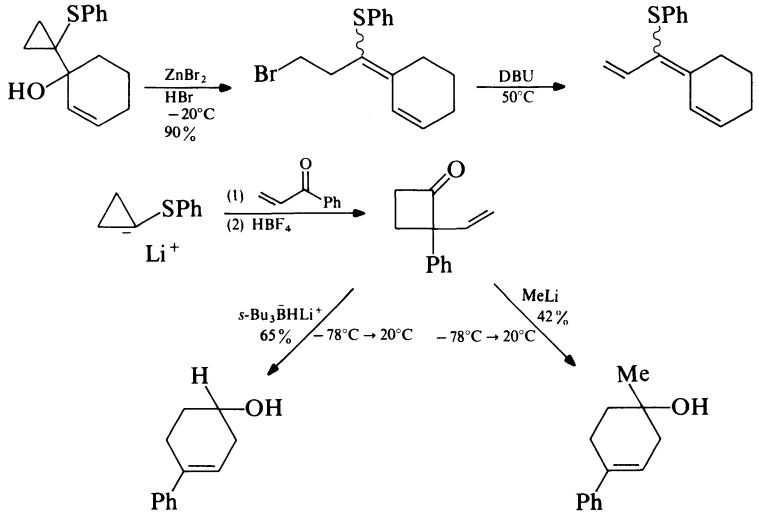
(106)

Alcohols formed in the initial step are transformed by employing Burgess reagent to 1-phenylthiocyclobutenes which can be desulphurized and hydrogenated to cyclobutanes, conrotatorily opened to 2-phenylthio-substituted dienes (equation 106) or converted to α,α-dibromocyclobutanone derivatives in effective procedures[222]. The 'normal' cyclopropyl–cyclobutyl rearrangement has been performed with different acid systems affording cyclobutanones directly, in high yield, and even with a high degree of stereoselectivity when being employed under appropriate conditions (equation 107). Interestingly, the stereochemical outcome of the ylide approach is complementary to the anion route described here. These methods constitute various modes of geminal dialkylations of a given carbonyl compound, which have been utilized for a grandisol synthesis[222] and in an approach to verrucarol[223].

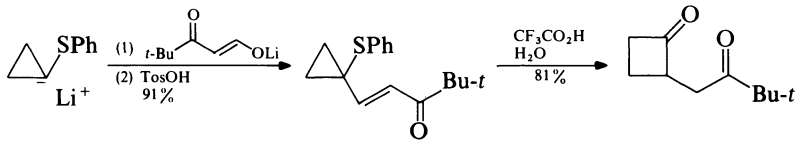


(107)

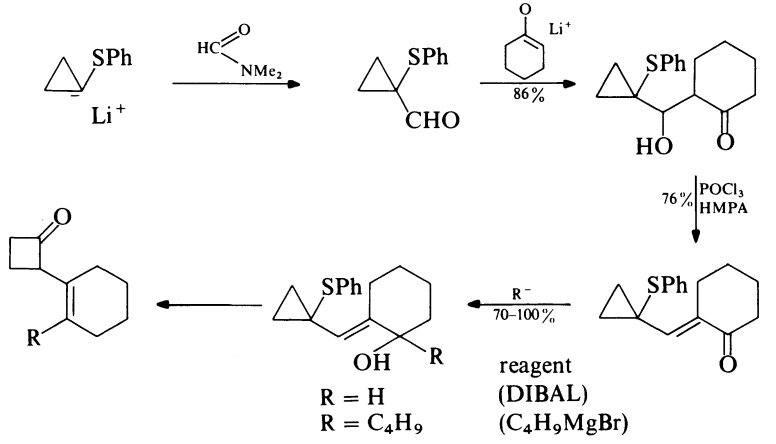
New ring-opening methods for phenylthio-substituted cyclopropylcarbinols generate intermediates with various possibilities for further transformation; an example is shown in equation 108[224, 225]. An overall [3 + 3]-annulation process is offered by combination of the Trost route to 2-vinylcyclobutanones and an alkoxy-accelerated rearrangement (equation 109)[226].



Reactions of phenylthiocyclopropyl lithium with alkyl halides and epoxides have also been reported to deliver products opened to a variety of carbonyl derivatives[227]. β-(1-Phenylthio)cyclopropyl enones have been prepared by using lithium salts of α-hydroxymethylene ketones as electrophiles and dehydrating with acid (equation 110). Rearrangement to cyclobutanones occurs with trifluoroacetic acid, whereas thermal vinylcyclopropane–cyclopentene expansion sometimes gives mixtures of regioisomers[228].

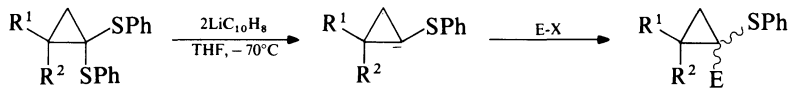


A different approach to these enones had earlier been developed by Trost and Jungheim who employed 1-formyl-1-phenylthiocyclopropane as electrophile in aldol reactions with ketone enolates (equation 111)[229]. The aldehyde required for this route can be prepared



by formylation of the lithiocyclopropane; however, syntheses of derivatives with other thioaryl groups—essential for some of the subsequent reactions—follow other paths. Equation 111 depicts transformation of dehydrated aldol adducts to allyl alcohols finally forming 2-vinylcyclobutanones by acid treatment. Further fragmentation reactions of these intermediates[229] are beyond the scope of this chapter.

As mentioned above, one major drawback of the Trost methodology is its restriction to the parent compound. It was the Cohen group who found an alternative approach to phenylthiocyclopropyl lithium chemistry by using a reductive lithiation of readily accessible cyclopropanone dithioketals which also works for alkyl-substituted cyclopropanes. The anions obtained by reduction with two equivalents of lithium naphthalene[230] or preferably lithium 1-(dimethylamino)naphthalene (LDMAN)[231] can effectively be trapped by apt electrophiles (equation 112).

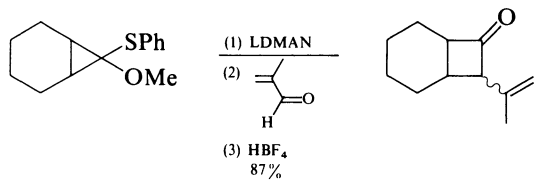


R^1, R^2 = H, Me

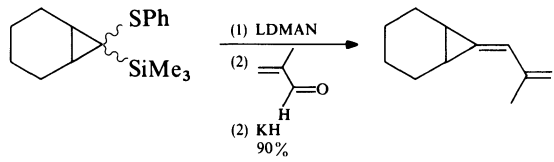
E = CO_2H, RCHOH, Me

(112)

This principle also allows generation of other very useful 1-hetero-substituted 1-lithio cyclopropanes, e.g. methoxy derivatives[232], which, after treatment with carbonyl compounds and acid, afford 2-vinylcyclobutanones in excellent yields (equation 113). The latter have been expanded to cyclopentenones and cyclohexenones by various methods[233–235]. On the other hand, trimethylsilylcyclopropanes undergo a Peterson-type olefination with aldehydes giving alkylidene cyclopropanes (equation 114)[236].

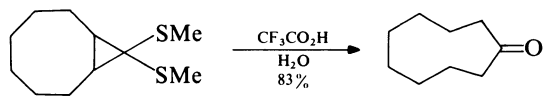


(113)



(114)

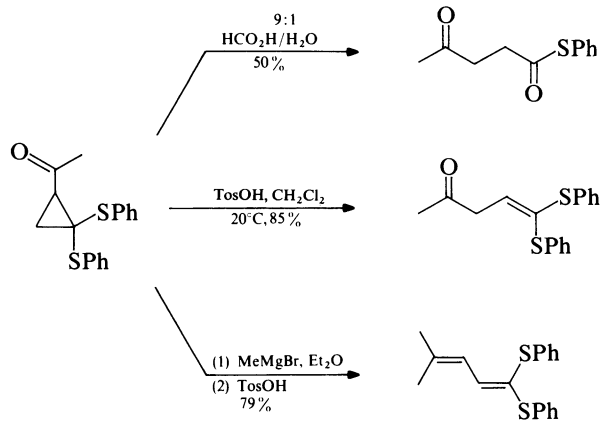
An allylidene cyclopropane synthesized via phenylthiocyclopropyl lithium has served as a potent diene in a Diels–Alder reaction[237]. Earlier, several methods for ring-opening of cyclopropanone dithioketals—one leading to ketones (equation 115)—had been reported[238].



(115)

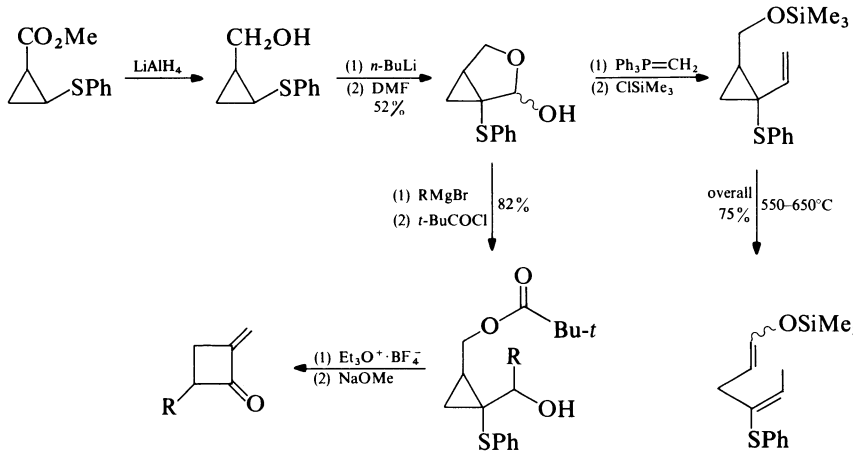
2. *Bifunctional sulphur-substituted cyclopropanes*

As is the case for oxycyclopropanes extra activation and extended product functionality is achieved by using sulphur-substituted cyclopropanes with a vicinal acceptor group. According to equation 116 synthesis of a variety of γ-oxothioesters and β-oxoketene dithioacetals is possible[239]. A formylcyclopropane of this type has been converted to a furan derivative[240]. Transformation of the carbonyl to a hydroxymethyl group and acid treatment allows preparation of dienes[241, 242].



(116)

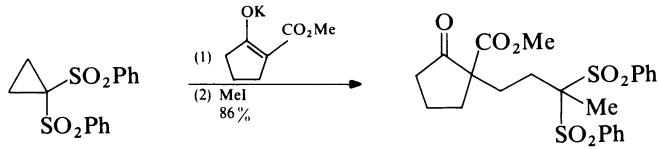
A bicyclic γ-lactol—accessible in a few steps—allows entry into certain vinylcyclopropanes (equation 117). At high temperature, these suffer a hydrogen shift to 1,4-dienes, which are masked 1,4-dicarbonyl compounds capable of many synthetically valuable selective reactions[243]. A total synthesis of trisporic acids profits from this approach[244]. If simple Grignard reagents are added to the γ-lactol, manipulation of the resulting cyclopropylcarbinols opens a path to 2-methylenecyclobutanones[245].



(117)

3. Other sulphur-substituted systems

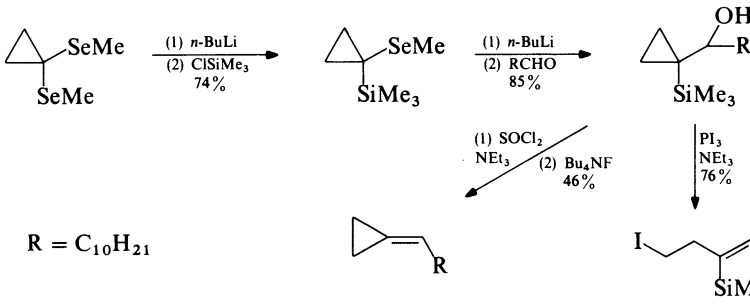
In certain aminocyclopropanes (see Chapter 22 of this volume) the acceptor quality of a sulphoxide or sulphonyl substituent[246] will allow ring cleavage under relatively mild conditions. α,β-unsaturated aldehydes are available by ring-opening of 1-alkoxy-substituted 2-benzenesulphonylcyclopropanes which can be substituted by deprotonation and alkylation α to the sulphonyl function[247]. Preparatively more important, however, is the strongly electrophilic 1,1-bis(benzenesulphonyl)cyclopropane which is opened by O, S, N- and C-nucleophiles, e.g. cuprates and enolates of β-ketoesters (equation 118)[248]. The sulphonyl groups make these adducts adaptable intermediates apt for a broad range of further transformations.



(118)

4. Selenium-substituted cyclopropanes

Despite the high toxicity of selenium compounds there has been a lot of activity in this field during the last decade. Not surprisingly, selenium-substituted cyclopropane derivatives have also been recommended for synthetic purposes[249]. An example is disclosed in equation 119[250]; one should remember, however, that most transformations can be achieved by other and less poisonous reagents.



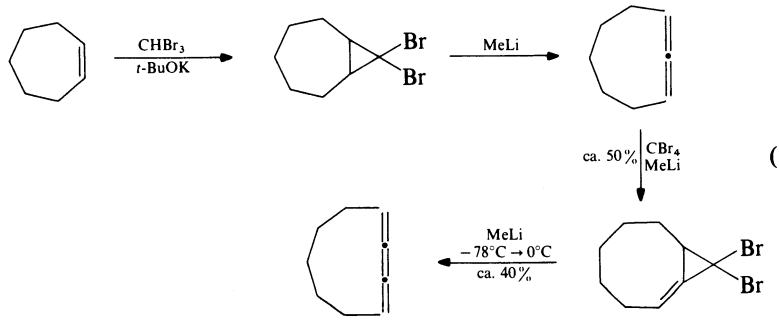
(119)

E. Halogens as Heteroatoms

Dihalocyclopropanes are easily available starting materials for many reactions of synthetic use. Their chemistry has become the subject of a detailed review article[17] covering work until 1980. This section can therefore be restricted to principles and recent developments.

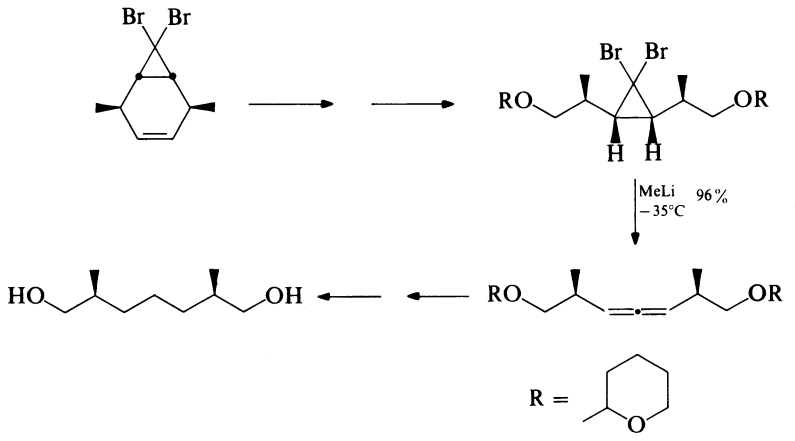
1. Halocyclopropanes as carbenoid precursors

Shortly after discovery of a convenient dihalocyclopropane synthesis[251] their conversion to allenes was effected[252]. This area has been reviewed very recently[253,254], and therefore only some very new examples will be mentioned[255,256]. Employing a repetitive cyclopropanation/allene formation sequence, 1,2,3-cyclononatriene—presumably the smallest isolable cyclic butatriene—has become available (equation 120)[257].



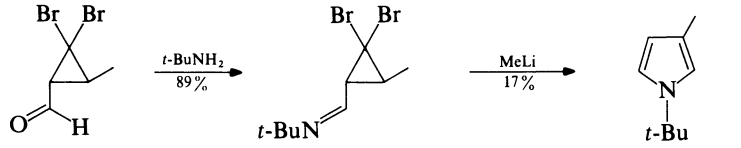
(120)

A stereocontrolled synthesis of the vitamin E side chain alcohol was achieved in an elegant fashion (equation 121) allowing mutation from a 1,4- to a 1,5-acyclic stereoselection process applicable also to the optically active series[258].



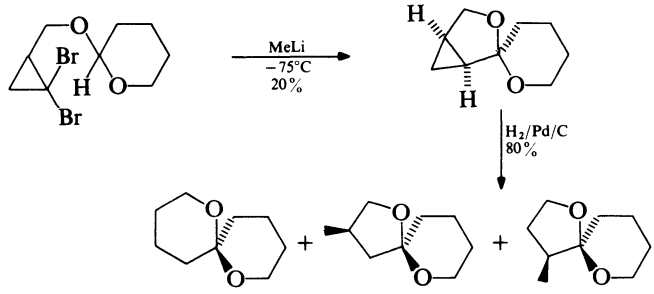
(121)

After treatment with alkyllithium reagents, dihalocyclopropanes bearing vicinal vinyl or imino groups can undergo carbene–carbene rearrangements. This quality was utilized, for instance, for generation of 1,5-dihydropentalene[259] and synthesis of pyrroles (equation 122)[260, 261].



(122)

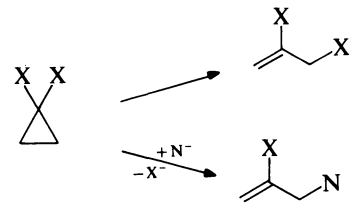
Insertion of a carbenoid into a C–H bond has also been performed under synthetic conditions[262]. A recent novel approach to spiroacetal pheromone (equation 123)[263] is unfortunately hampered by the absence of regioselectivity in the ultimate cyclopropane hydrogenation step (see Section III.A).



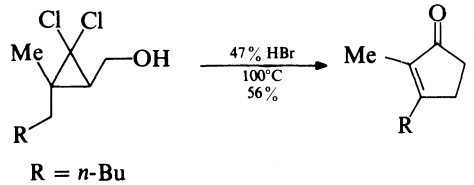
(123)

2. *Halocyclopropanes in ring-openings to allyl derivatives*

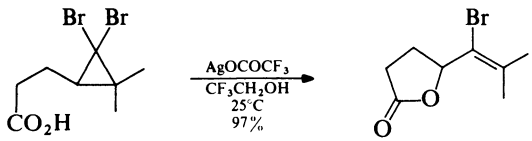
The opening of halocyclopropanes to allyl systems according to equation 124 can happen thermally or with the assistance of electrophiles and nucleophiles[117]. Some recent examples include an efficient cyclopentenone synthesis (equation 125)[264], an electrocyclic opening/cyclization sequence giving functionalized furan and pyran derivatives (equation 126)[265], an elegant total synthesis of the 'very fast death factor' alkaloid (±)anatoxin *a*[266], and a nice application of the well known nucleophilic opening[267] to the preparation of crystalline methylene aziridines (equation 127)[268].



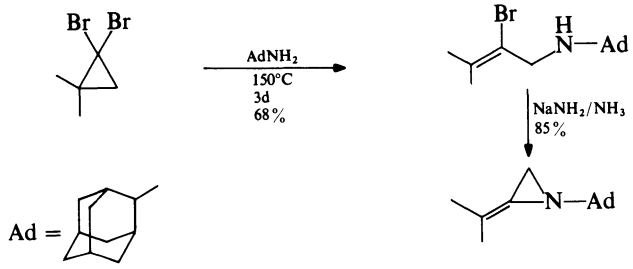
(124)



(125)



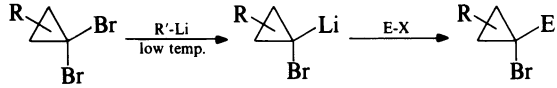
(126)



(127)

3. Metalation of halocyclopropanes

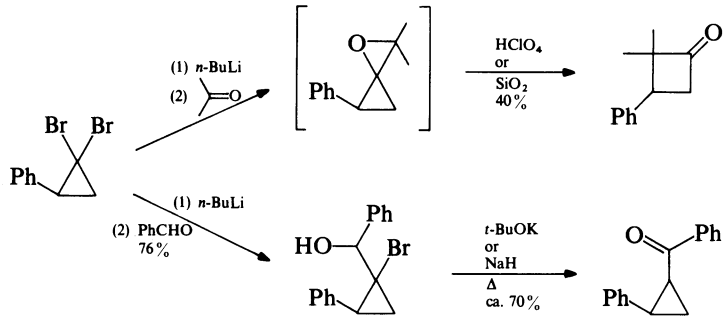
A good deal of the preparative utility of dihalocyclopropanes arises from the easy halogen–metal exchange[269]. The corresponding carbanion (lithium carbenoid[270], see Section VI.E.1) can be trapped at low temperature by a variety of electrophiles, resulting in substituted or functionalized halocyclopropanes (equation 128).



(128)

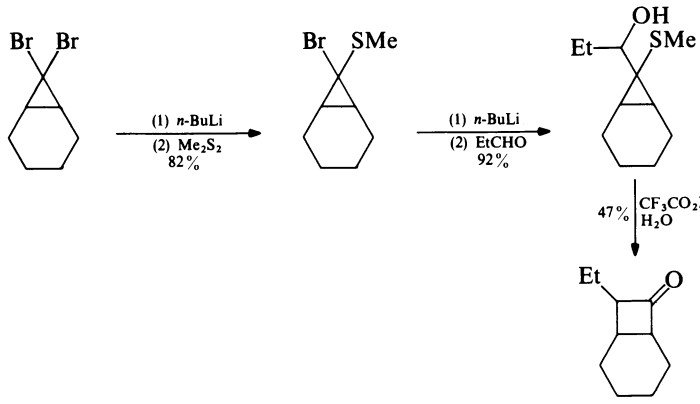
E = CO_2H, $SiMe_3$, alkyl, RCHOH . . . .

The rich, synthetically valuable chemistry of these carbanions is mainly due to the independent efforts of two groups[271–273]. As outlined in equation 129 addition of a ketone to the carbanion is the basis for the preparation of cyclobutanones obtained after acid treatment of the intermediate oxaspiropentanes. In contrast, aldehydes as electrophiles give isolable bromoalcohols, which undergo redox isomerization to cyclopropyl ketones.



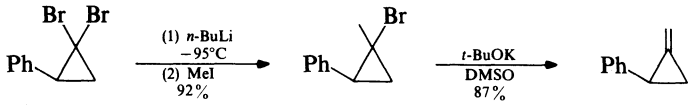
(129)

Regio problems can arise if aromatic ketones are involved in the cyclobutanone synthesis, and aldehydes can only be forged into the cyclobutanone skeleton by detouring via methylthio-substituted cyclopropanes (equation 130)[271].

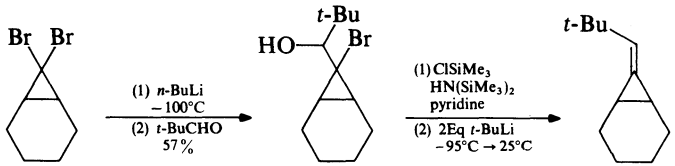


(130)

Preparation of alkylidene cyclopropanes is feasible by alkylation of lithium carbenoids followed by base-promoted elimination (equation 131)[274], or by addition of carbonyl compounds, silylation and reductive elimination (equation 132)[275]. Similarities with the chemistry displayed by sulphur-substituted cyclopropanes (Section VI.D.1) are obvious.

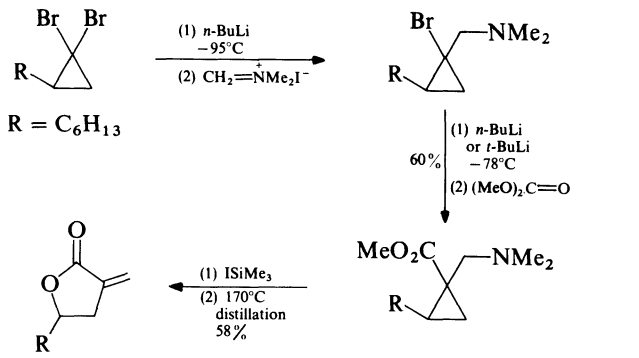


(131)



(132)

Following these examples, methylene cyclopropene[276] and certain 5,6-dihydrocalicenes[277] are now obtainable. Adding lithio trimethylsilylcyclopropanes to aldehydes also provides alkylidene cyclopropanes (Peterson olefination route)[278]. An approach to α-methylene γ-butyrolactones starting with dibromocyclopropanes has been opened by a suitable manipulation of intermediate cyclopropyl anions (equation 133)[279].

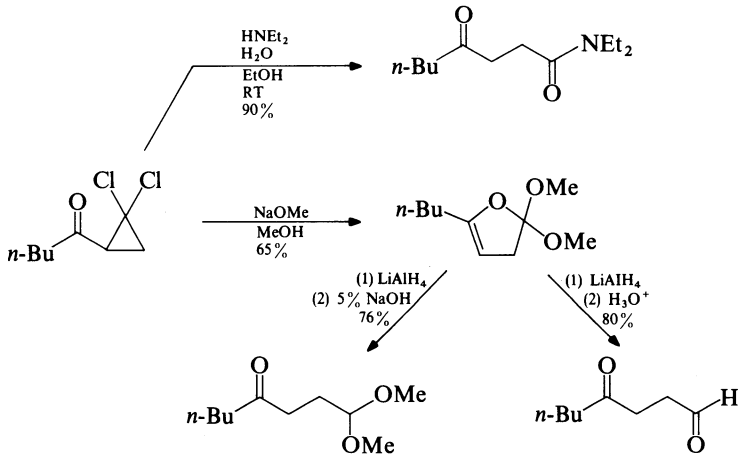


(133)

Certain cyclopropylmethyl acetates, synthesized from dibromocyclopropanes, have been reacted with various organoaluminium compounds affording cyclopropane derivatives and/or ring-opened products depending on the substituent pattern[280]. Dibromocyclopropanes with a chloromethyl or a mesyloxymethyl group undergoe a $Ni(CO)_4$-induced ring cleavage giving γ, δ-unsaturated carboxylic acid derivatives in the presence of alcohols or amines[281].

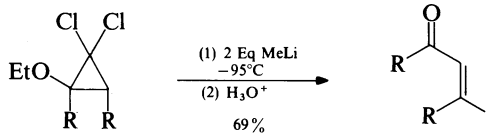
4. Halocyclopropanes activated by acceptor or donor groups

By treatment with sodium alkoxides or secondary amines gem-dihalocyclopropyl ketones will be converted to different 1,4-dicarbonyl compounds (equation 134)[282–284]. Similar reactions are known for sulphonyl-substituted dichlorocyclopropanes[285] and difluorocyclopropyl ketones[286].



(134)

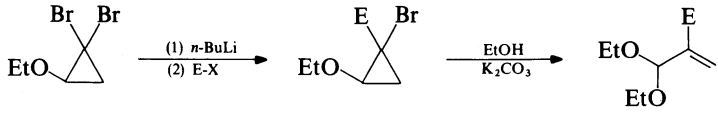
Donor-substituted halocyclopropanes are very versatile building blocks in organic synthesis. An early application which is demonstrated in equation 135 constitutes the overall transformation of an enol ether to a β-methyl α,β-unsaturated ketone[287], which in the case presented gives muscone after hydrogenation. A cyclopropene and allene are the proposed intermediates in this process.



(135)

R, R = $-(CH_2)_{12}-$

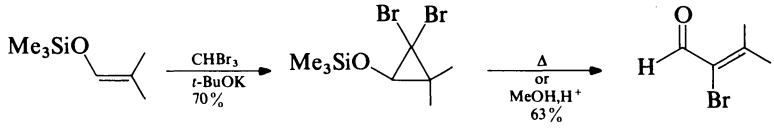
Solvolysis of 1-bromo-2-ethoxycyclopropanes, easily obtained from lithium carbenoids and electrophiles (equation 136), provides efficient access to α,β-unsaturated acetals or to their corresponding aldehydes by acidic workup. This methodology has been utilized for syntheses of the juvenile hormone (JH-II), β-sinsensal and jasmonoids[288].



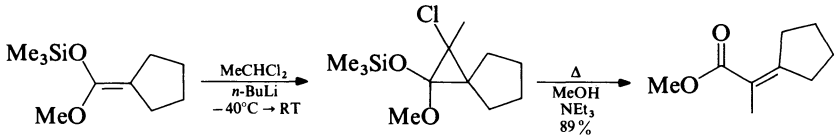
(136)

E = H, Br, $SiMe_3$, SPh, RCHOH

Again, much efficiency was gained by switching from alkoxy to siloxycyclopropanes[20]. Dibromocarbene addition to silyl enol ethers generates cyclopropanes which open to α-bromo α,β-unsaturated carbonyl compounds on thermolysis or treatment with acid in methanol (equation 137)[289,290]. It has been shown that this homologation process also works for siloxycyclopropanes obtained by addition of other carbenoids (equation 138)[291–294] and that it is useful for terpene preparation[295,296].

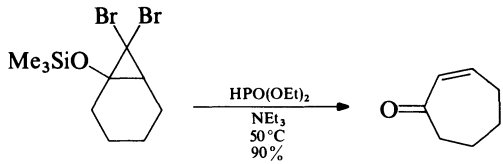


(137)



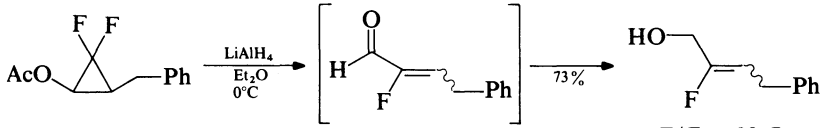
(138)

Reductive ring cleavage under mild conditions affords α,β-unsaturated ketones directly (equation 139)[297,298]. Also, various oxidative methods of dihalo oxycyclopropanes have been reported[299-301] but so far have won little synthetic use.



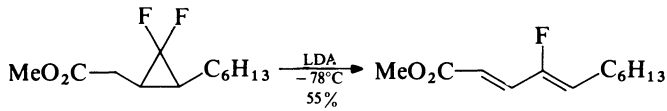
(139)

Reduction of acetoxy difluorocyclopropanes with lithium aluminium hydride allows preparation of β-fluoroalcohols (equation 140)[302], whereas deprotonation of difluorocyclopropanes bearing an acceptor-substituted side chain gives fluorodienes stereoselectively after cyclopropylmethylanion–homoallyl anion rearrangement and fluoride elimination (equation 141)[303].



$Z/E = 93:7$

(140)



$E,Z/E,E = 95:5$

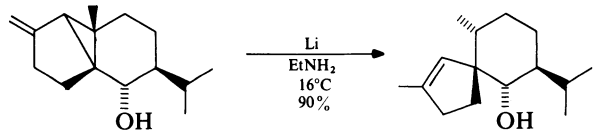
(141)

VII. VINYLCYCLOPROPANES

Since they are equivalent to homobutadienes, cyclopropanes interacting directly with an olefin unit display a particularly rich chemistry. Pericyclic reactions come into play in this specific area. Similar to other cyclopropane derivatives, the reactivity of vinylcyclopropanes with nucleophiles, electrophiles and radicals as well as their general chemical behaviour will be governed by substituents at the cyclopropane core and at the double bond[12].

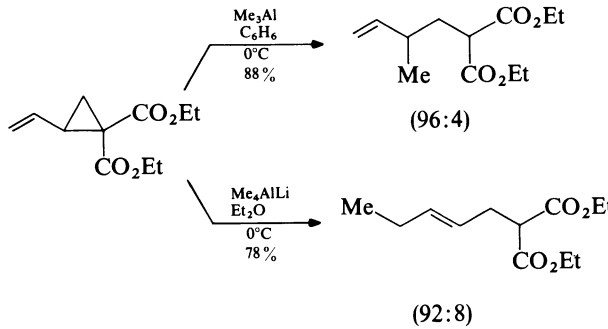
A. Additions of Nucleophiles, Radicals and Electrophiles to Vinylcyclopropanes

The electron is the smallest thinkable 'nucleophile' which—generated from lithium in ethylamine—is even able to open certain unactivated vinylcyclopropanes (equation 142); the spiro[4.5]decane so obtained could be converted into the isocyanide sesquiterpene (−)-axisonitrile-3, which has the opposite absolute configuration of a marine sponge constituent[304].



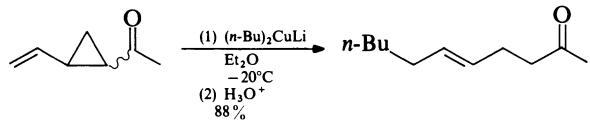
(142)

Nucleophiles will open acceptor-substituted vinylcyclopropanes either by attacking the three-membered ring resulting in a 1,5-addition or by a 1,7-addition to the olefin moiety[10,86]. In most cases two acceptor groups are a prerequisite for sufficient activation (see Chapter 9). An interesting nucleophile-dependent dichotomy is demonstrated by equation 143. Organoaluminium compounds add in a 1,5-fashion whereas the corresponding ate-complexes prefer the 1,7-mode[280].



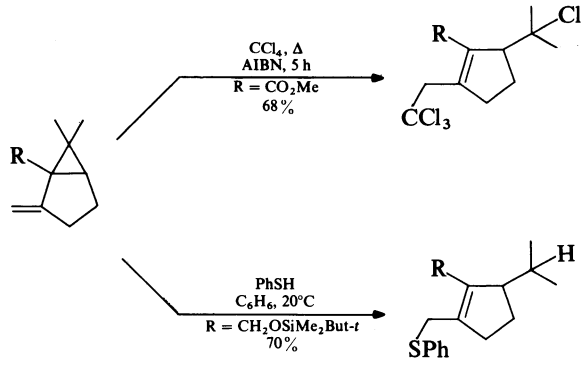
(143)

However, additions of nucleophiles to monoactivated vinylcyclopropanes are known, too. Cuprates provide γ,δ-unsaturated ketones in high yields as illustrated in equation 144[305], and reactions of trialkylboranes will occur as a free-radical chain process affording the same products with low efficiency.



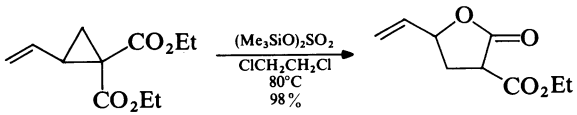
(144)

Beside these last-mentioned examples there are only a few reports dealing with the additions of free radicals to vinylcyclopropanes. Recent prototypes have been presented by the Paquette group (equation 145) showing that in this specific case regiochemistry is not influenced by the nature of the substituent R[306]. Earlier examples had employed tributyltinhydride as radical source[307] (see also equation 93). The field of radical additions to cyclopropanes may become important in synthetic organic chemistry similarly to free radical additions to olefins which were brought into play during the last years.



(145)

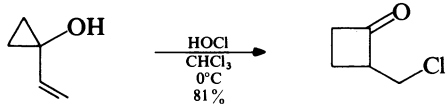
So far, however, electrophiles are more common tools for the cleavage of vinylcyclopropanes. The cyclopropanes, starting materials in equation 145, will also readily add electrophiles, leading to cyclopentene derivatives suitable for retigeranic acid synthesis[306]. One example of an acid-promoted ring expansion/annulation providing an α-methylene γ-butyrolactone is known[308]. Bis(trimethylsilyl)sulphate catalysis has been reported for conversion of certain cyclopropanecarboxylates to γ-butyrolactones (equation 146)[309]. This rearrangement also works with cyclopropanes lacking a vinyl group, although, sometimes, with low efficiency. With trimethylsilyl iodide a 1,7-addition has been observed.



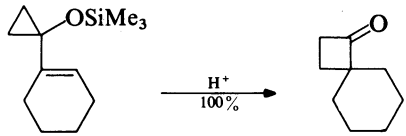
(146)

Vinylcyclopropanes and organomercury or thallium compounds are starting materials for a recent novel preparation of π-allyl palladium complexes[310] which can finally be converted to heterocycles[311].

Most importantly, additions of electrophiles to vinylcyclopropanes can lead to cyclobutanones if a suitably located donor substituent is present. It was Wasserman and coworkers who showed that vinylcyclopropanols—obtained from cyclopropanone hemiacetals and vinylmagnesium bromide—can be expanded to functionalized cyclobutanones (equation 147)[312].

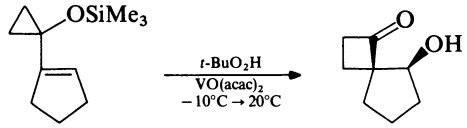


(147)



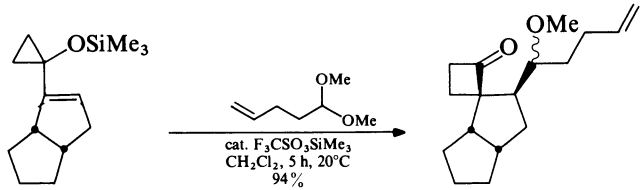
(148)

Due to efforts of Conia's (equation 148) and Trost's groups access to more substituted vinylcyclopropanes has been gained operating with siloxy derivatives prepared either by Simmons–Smith cyclopropanation[313] or using diphenylsulphonium cyclopropylide as a key substance[217] (see Section VI.D.1). Oxidative rearrangement has led to a cyclopentanol



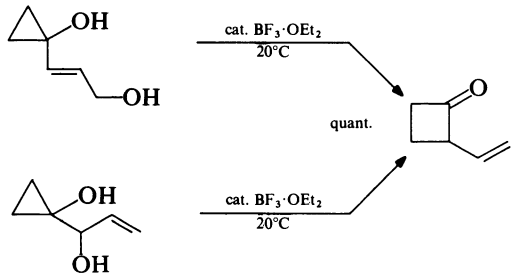
(149)

(equation 149)[314], benzeneselenenyl bromide has been employed in a recent synthesis of plumericin[315], and Lewis acid-catalysed additions of acetals allow even C–C formation, finally completing a 1,1,2-trialkylation of a ketone in a stereoselective manner (equation 150)[316].



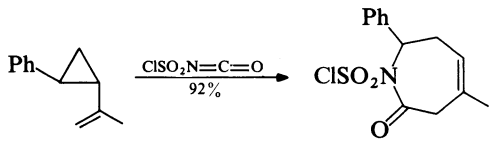
(150)

2-Vinylcyclobutanone as well as more substituted derivatives are available from different diols by BF_3 etherate-induced rearrangement (equation 151)[317,318].



(151)

Cycloadditions of electrophilic olefins or cumulenes to vinylcyclopropanes should also be mentioned in this context, since in most cases stepwise reactions starting with an electrophilic attack are very likely. One example operating with chlorosulphonyl isocyanate and providing a seven-membered lactam is depicted in equation 152[319]; however, so far most reactions in this area have a limited synthetic potential.



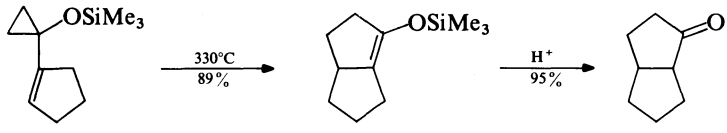
(152)

B. Thermal Rearrangements of Vinylcyclopropanes

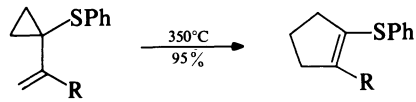
1. Vinylcyclopropane–cyclopentene rearrangement

This field has been exhaustively reviewed[22] as late as 1985 and is also treated in Chapter 13. Therefore only a few highlights of this intriguing method creating cyclopentene derivative—a class of compounds which attracted much attention during the

last decade—will be discussed here. Again, Conia[5,16,320] and Trost[3,321] made major contributions applying siloxy- or sulphur-substituted vinylcyclopropanes in this reaction (equations 153 and 154) thus providing cyclopentenes with functions ready for further transformations. The availability of a siloxycyclopropane and its expansion to a cyclopentene via the cyclopropylide approach has been essential in a synthesis of the diterpene aphidicoline[322].



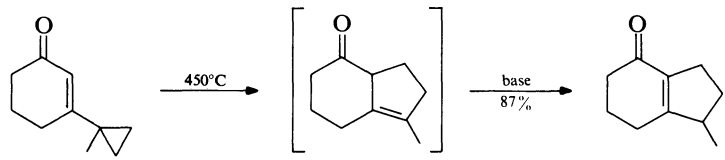
(153)



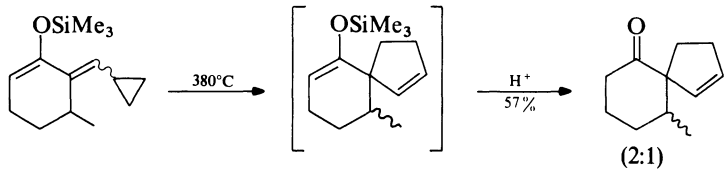
(154)

$R = C_6H_{13}$

The first of two annulation steps required for the preparation of zizaene has been effected by the Piers group employing thermal rearrangement of a β-cyclopropyl-α,β-unsaturated ketone as outlined in equation 155[323]. The starting material is accessible by addition of a cyclopropylcuprate to the corresponding β-iodoenone. Similarly, spirovetivanes have been obtained in a sequence comprising pyrolysis of 2-(cyclopropylmethylene) cycloalkanones and their corresponding silyl enol ethers (equation 156)[324]. Other siloxycyclopropanes substituted by an enone moiety give an alternative entry into this class of terpenes using the same pivotal reaction[318].



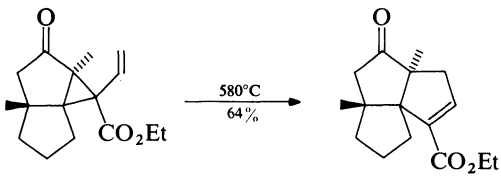
(155)



(156)

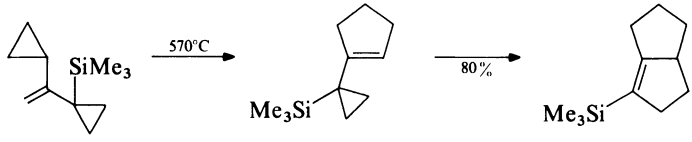
(2:1)

The Hudlicky route making vinylcyclopropanes by intramolecular carbene additions to dienes has led to a variety of polycyclic cyclopentanoic terpenes. The crucial step in a synthesis of isocomenic acid is illustrated by equation 157[325].

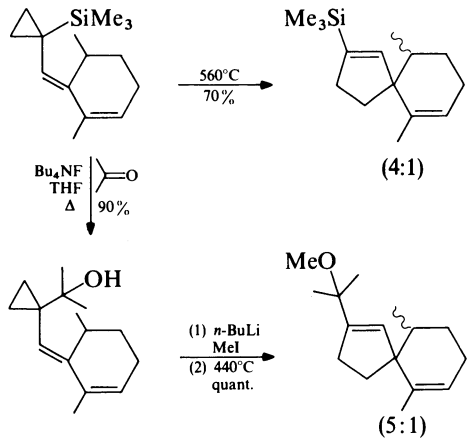


(157)

Paquette and his students have recently developed several different methods to prepare trimethylsilyl vinylcyclopropanes, which can contain additional functional groups, and have investigated the thermal behaviour of these compounds[326,327]. As an important result the order of rearrangements as shown in equation 158 has been established, clearly demonstrating that the trimethylsilyl group retards vinylcyclopropane–cyclopentene ring expansion[326]. Products of this and more complex types are flexible intermediates, since the vinylsilane unit allows regioselective reactions with electrophiles. Employing this strategy, access to spirocyclic terpenes is provided (equation 159)[328].



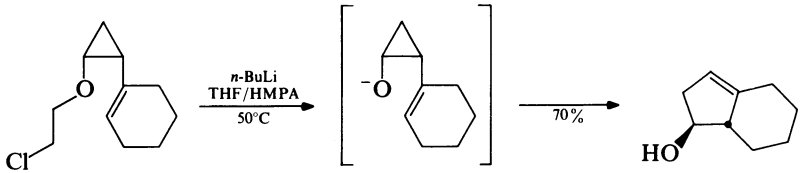
(158)



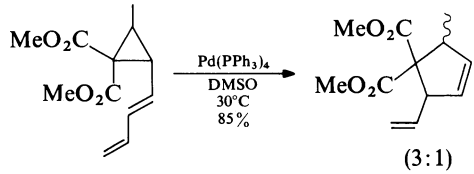
(159)

Interestingly, a pentadienyl anion can be generated by fluoride treatment and trapped with acetone, the resulting product rearranges at a considerably lower temperature, albeit without significant improvement of stereoselectivity[328].

Two ingenious possibilities to perform the ring expansion at low temperature are displayed in equations 160 and 161, the first using the trick of alkoxy acceleration[329], the second employing Pd(0) catalysis[330]. The latter principle, which works only for derivatives having a dienyl unit and two acceptor groups, could be applied to syntheses of dolichodial and iridiol. A similar dienylcyclopropane–vinylcyclopentene rearrangement promoted by diethylaluminium chloride at 0°C has been used by Corey and Myers in their synthesis of the 'Antheridium-inducing factor' ($A_{AN}2$)[331].



(160)

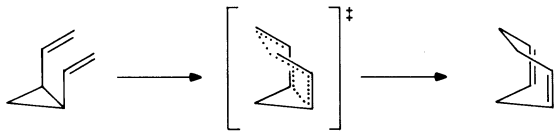


(3:1) (161)

2. *Divinylcyclopropane–cycloheptadiene rearrangement*

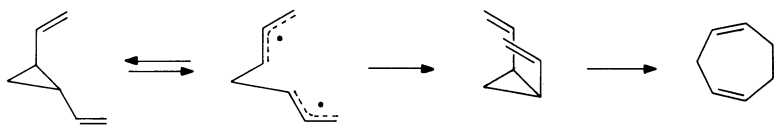
Although the Cope rearrangement[332] of *cis*-1,2-divinylcyclopropanes to 1,4-cycloheptadienes has been known since the early 1960s as a particular case of $[\sigma_s^2 + \pi_s^2 + \pi_s^2]$ processes, it took more than ten years to recognize the synthetic potential of this reaction. Since the field has not adequately been reviewed so far, a closer insight into this important rearrangement forming seven membered carbocycles should be justified within this account.

By a kinetic study Schneider and Rau[333] made it evident that Cope rearrangements of this type had to pass via a boat-like transition state as depicted in equation 162. Of course, this stereoelectronic requisite has certain consequences for synthetic applications, particularly for highly substituted systems.



(162)

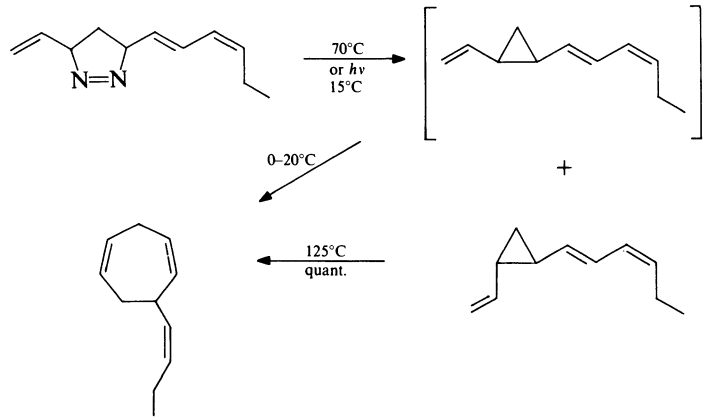
Whereas rearrangement of *cis*-1,2-divinylcyclopropanes often occurs at temperatures as low as 0–20°C, the corresponding *trans* compounds require considerably higher temperatures (100–250°C). The reason for this is that a direct Cope expansion could give only a 1,4-cycloheptadiene containing two *trans* double bonds. This is why a homolytic cleavage of the central cyclopropane bond has to be assumed, giving two allyl radicals able to recombine either to the starting material or, after rotation, to the *cis* compound (equation 163)[334].



(163)

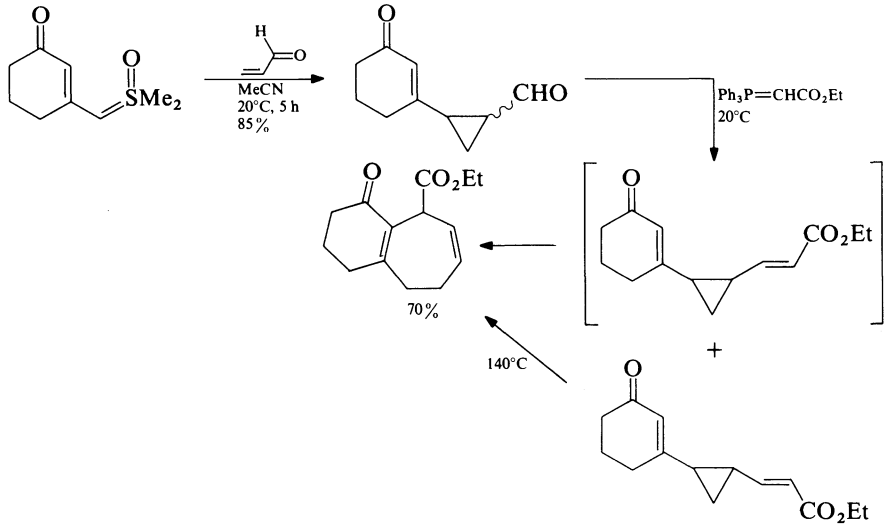
The latter will consequently undergo the usual concerted sigmatropic process finally resulting in the cycloheptadiene derivative. Due to the higher temperature needs and to the participation of radical intermediates, side reactions are more likely to occur in the *trans* series.

Early synthetically oriented divinylcyclopropane–cycloheptadiene rearrangements were performed with hydrocarbons[335, 336], and were in part due to the interest in syntheses of marine brown algae constituents[337]. The preparation of ectocarpene[338] is displayed in equation 164. The corresponding divinylcyclopropanes have either been constructed by Wittig methodology[337] or, as in the case shown, by addition of diazoalkanes to apt polyenes followed by photolysis or thermolysis[338].



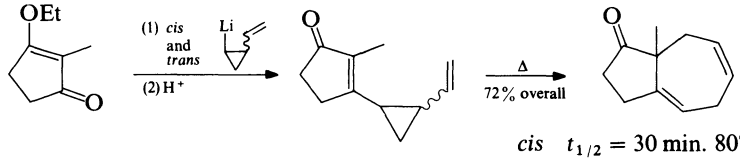
(164)

Marino, Piers and Wender have made major contributions to the advancement of more functionalized divinylcyclopropanes allowing preparation of targets with higher complexity. As a result they could apply the methods developed to a variety of elegant terpene syntheses. Marino and coworkers used allyl sulphoxonium ylides for construction of vinylcyclopropanes (equation 165), which after Wittig reaction of the aldehydes form mixtures of *trans*-1,2-divinylcyclopropanes together with the corresponding cycloheptadienes. After heating the mixture these have been obtained in a pure state[339–342]. This sequence has also allowed preparation of a 4a*H*-benzocycloheptene derivative[343].



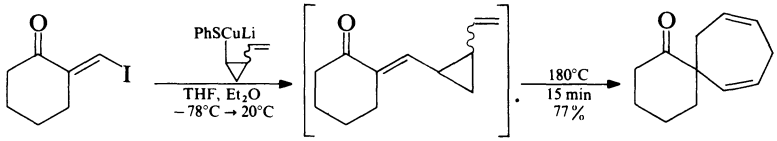
(165)

1-Metallo 2-vinylcyclopropanes were introduced independently as a tool for the efficient preparation of 1,2-divinylcyclopropane skeletons in 1976 by the three groups mentioned above[344–347]. Either 2-vinylcyclopropyl lithium addition to 3-alkoxyenones[344,347] followed by acid treatment will lead to the desired rearrangement precursors (equation 166), or the corresponding cyclopropyl cuprates will add to β-iodoenones[345,348] and electrophilic acetylenes[347] forming directly divinylcyclopropanes (equation 167).



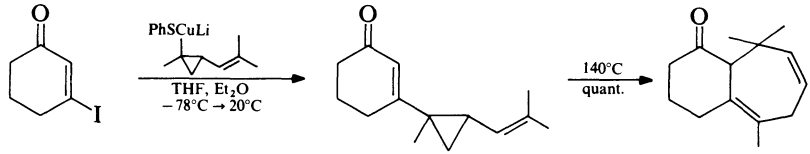
(166)

cis $t_{1/2}$ = 30 min. 80°C
trans $t_{1/2}$ = 30 min. 160°C

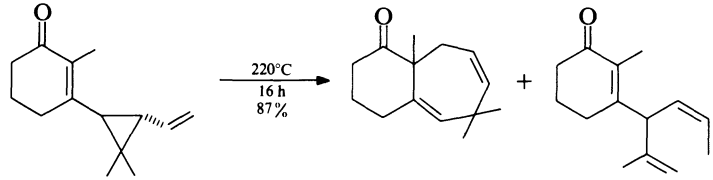


(167)

Piers and Ruediger have smartly used this basic reaction (equation 168) for a synthesis of the sesquiterpenoid β-himachalene[349]. However, loading the systems to be rearranged with alkyl groups can considerably decelerate the Cope process with the result of competing homo[1, 5]-sigmatropic hydrogen shift in the *trans* compounds (equation 169)[347, 348, 350–352].



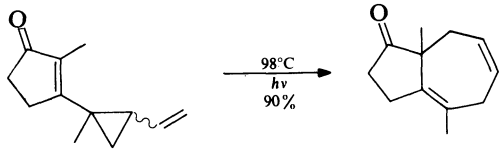
(168)



(169)

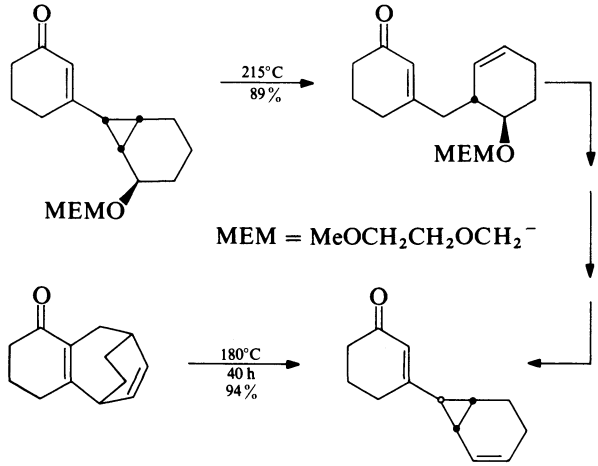
1:4

Wender and coworkers could ingeniously solve this problem in their approach to damsinic acid and confertin by *simultaneous* irradiation and thermolysis giving the desired cycloheptadiene derivative contaminated by traces of H-shift products only[352] (equation 170).



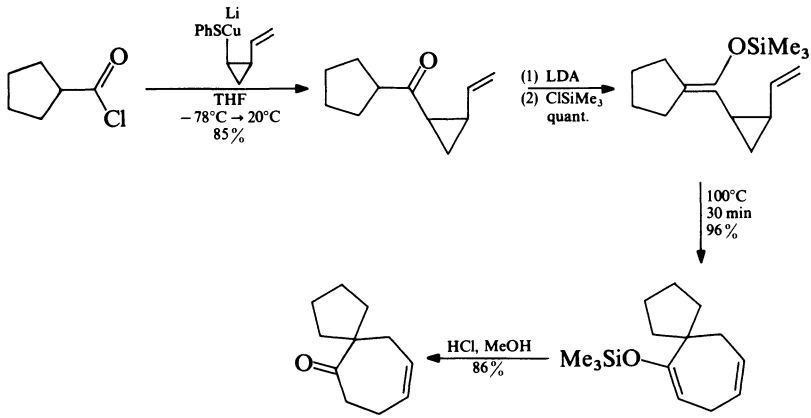
(170)

Bridged tricyclic compounds are available by combining the homo-[1, 5]-hydrogen migration (followed by a proton-shift) with the Cope rearrangement occurring a few steps later (equation 171)[350]. A functionalized linear annulated tricyclic compound should have high potential to enter the tiglane, daphnane and ingenane families[353].



(171)

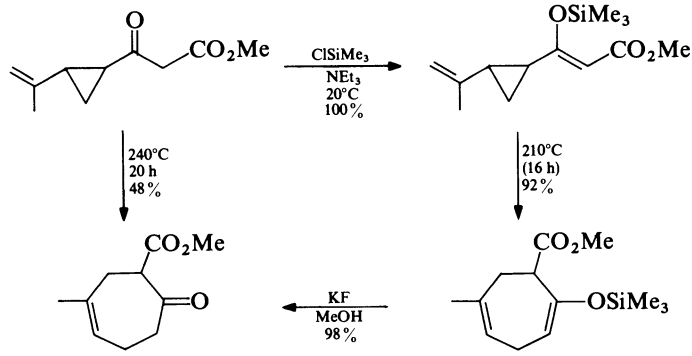
An alternative way to generate a divinylcyclopropane system takes advantage of enolizable carbonyl groups. Trapping of the enolate with trialkylsilyl chloride[344, 354] will usually create the second olefin unit required for a Cope rearrangement. The example of equation (172) demonstrates a sequence of high overall efficiency providing silyl enol ethers which have been hydrolysed to 4-cycloheptenones[354]. The enol ethers should also be versatile intermediates for other transformations.



(172)

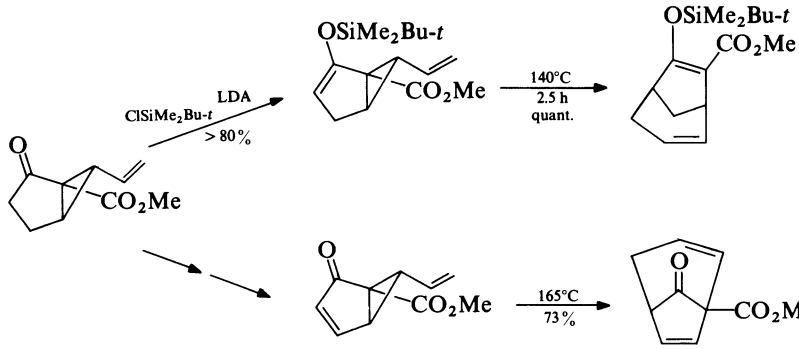
It is also feasible to start with a mixture of *cis*- and *trans*-cuprate provided that higher temperatures (230°C, 30 min) are applied for complete ring expansion[355].

Similarly, a vinylcyclopropyl ketoester can be converted to a substituted 4-cycloheptenone as outlined in equation 173. Direct thermolysis via the ketoester enol requires somewhat higher temperatures and occurs with moderate yield[356].

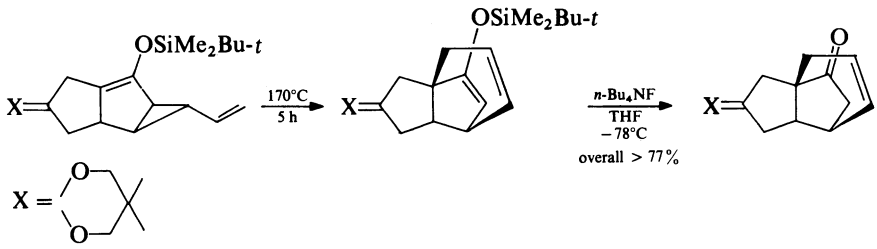


(173)

The bicyclic cyclopropyl ketone shown in equation 174—easily accessible from the corresponding diazocarbonyl compound—could be transformed into two bicyclic divinylcyclopropanes with different functionality and positioning of the cyclopentene double bond. Rearrangement of these compounds leads to the bicyclo[3.2.1]octane series[357, 358]. Very recent syntheses of the terpenes sinularene[359] and quadrone include a pivotal Cope process of divinylcyclopropanes generated and rearranged in an analogous fashion (equation 175)[360].

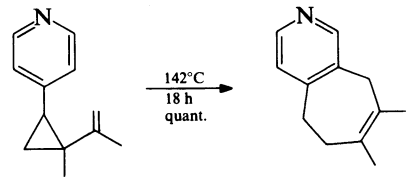


(174)



(175)

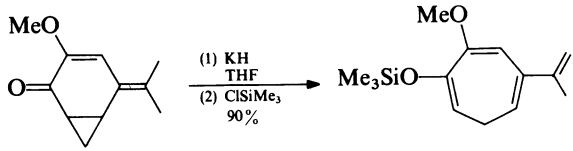
A total synthesis of karahanaenone could be performed expanding a divinylcyclopropane generated by free radical addition of thiophenol to an alkenylidenecyclopropane, however with low efficiency[361]. Preparations of fused heterocycles are possible if a heteroaromatic system is taking part in the sigmatropic process (equation 176). Additional examples demonstrate the accelerating effect of *N*-methylation[362].



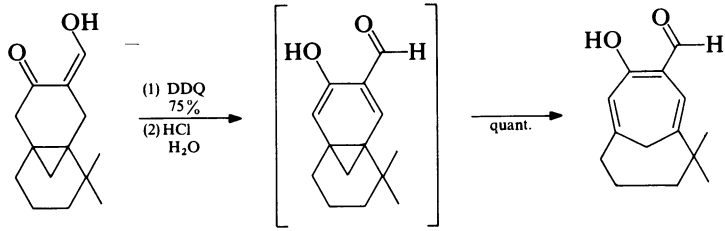
(176)

The potential of this approach for heterocycle preparation has by far not been exhausted, as is the case for systems containing other or more heteroatoms within the frame executing the Cope rearrangement[363].

Two unique ring enlargements which can also be classified as divinylcyclopropane–cycloheptadiene expansions are shown in equations 177[312] and 178[364]. The last reaction has been employed for constructing the 1,6-methano[10]annulene carbon skeleton required for the unusual furanosesquiterpene dihydrospiniferin-1[364].



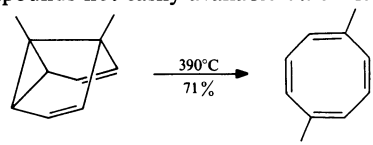
(177)



(178)

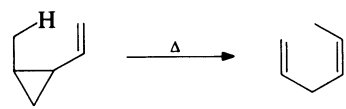
3. Other thermal reactions

Rearrangements of semibullvalenes to cyclooctatetraene derivatives as illustrated in equation 179 lead to compounds not easily available otherwise[365, 366].

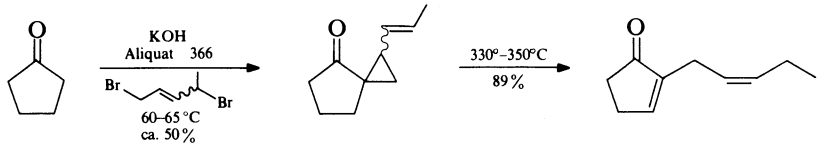


(179)

Homo[1, 5]-hydrogen shifts affording 1,4-dienes (equation 180)[367] have so far not often been applied for synthetic purposes, one exception being the sequence outlined in equation 181. It forms a cyclopentenone which allows large-scale preparation of the odorants methyl jasmonate and *cis*-jasmone[368, 369].



(180)

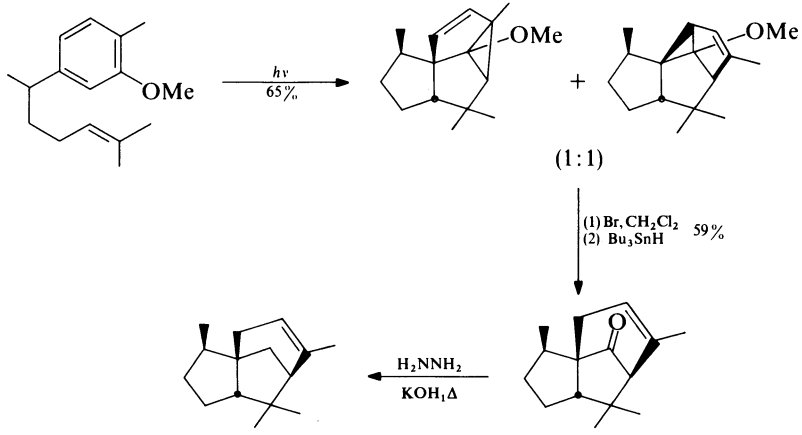


(181)

The influence of substituents on the regiochemistry of this type of vinylcyclopropane openings has recently been studied by Piers and his students[350, 370, 371]. Their results might help to recognize and utilize the synthetic potential of this route to 1,4-dienes[372] (see also equation 117).

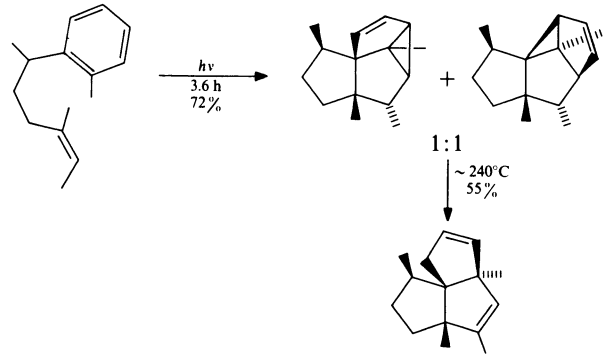
C. Miscellaneous Reactions of Vinylcyclopropanes

Various reactions discussed so far have been applied to cleave complex vinylcyclopropanes which are available by a novel method of extreme convergency. In 1981 Wender and Howbert reported their first example for an intramolecular 1,3-photoaddition of an olefin unit to an adjacent arene moiety[373]. This ingenious strategy generates functionalized polycyclic vinylcyclopropanes in a regio- and stereocontrolled fashion which is perfect to synthesize certain terpenes. The key steps of a short route to α-cedrene are displayed in equation 182[373].



(182)

Similarly, the isocomene skeleton has effectively been assembled by photoaddition, followed by homo[1, 5]-hydrogen shift breaking the vinyl cyclopropane (equation 183)[374].

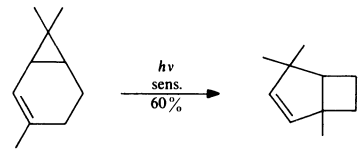


(183)

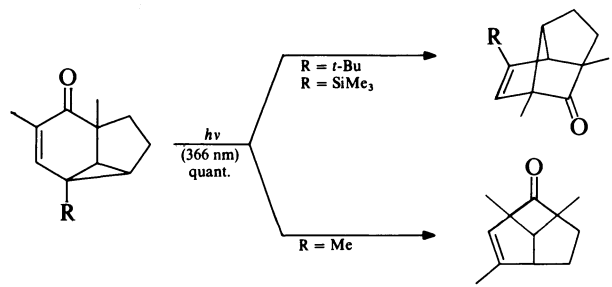
Additional applications of this intriguing method to create polyquinanes include synthesis of hirsutene[375], modhephen[376], and silphinene[377] employing acid-induced or reductive cleavage of a vinylcyclopropane and opening of a cyclopropyl ketone with a

cuprate. Total synthesis of silphiperfol-6-ene and related compounds take advantage of the rarely used (see Section VII. A) radical addition to a vinylcyclopropane, which has been generated again by the crucial arene photocycloaddition[378]. This methodology has also been fruitful in an approach to [5.5.5.5]fenestranes[379]. The well known intermolecular version of 1,3-photocycloadditions delivers products of lower complexity and is by far less effective when yields, regio- and stereoselectivity are regarded[380].

Photochemical vinylcyclopropane–cyclopentene rearrangements[22] open an alternative to prepare racemic grandisol from (optically active) Δ^2-carene[381] (equation 184). On the other hand, irradiation of tricyclic enones has resulted in two different product types as shown in equation 185, depending on the nature of substituent R; both classes of compounds should be of synthetic value[382, 383].

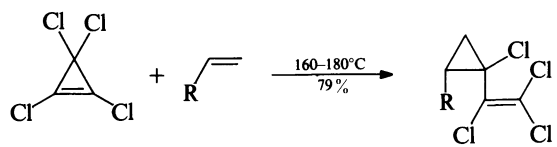


(184)



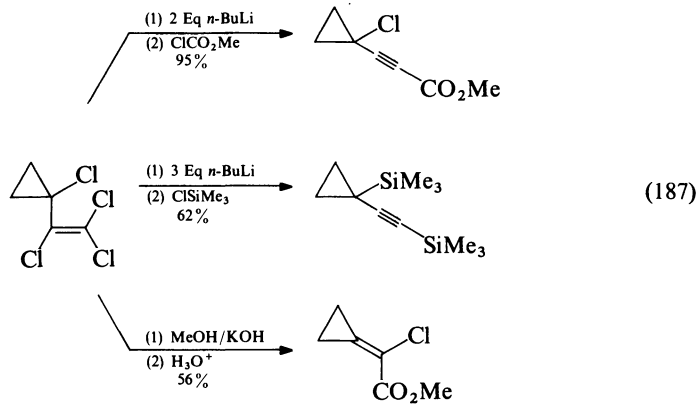
(185)

The de Meijere group has demonstrated that tetrachlorocyclopropene is a very convenient source for tetrachlorovinylcarbene, which could be trapped by a variety of olefins and provides an array of interesting chlorinated vinylcyclopropanes (equation 186)[384]. Preparations starting from other precursors have also been reported[385, 386].



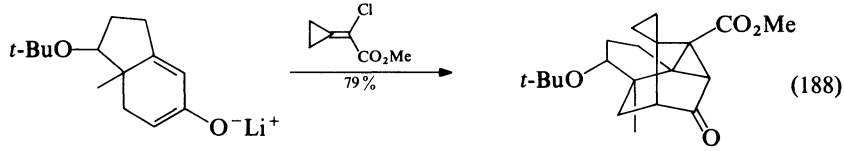
(186)

The reactivity of these promising building blocks has very recently been reviewed by de Meijere[21], therefore only a few principles will be discussed in this text. Treatment with *n*-butyllithium as outlined in equation 187 will give certain functionalized alkynylcyclopropanes[387, 388], which can serve as active components in cycloadditions or reactions with olefins in the presence of $Co_2(CO)_8$. The latter [2 + 2 + 1]-addition provides cyclopropyl cyclopentenones[389] capable of undergoing vinylcyclopropane–cyclopentene rearrangement.



(187)

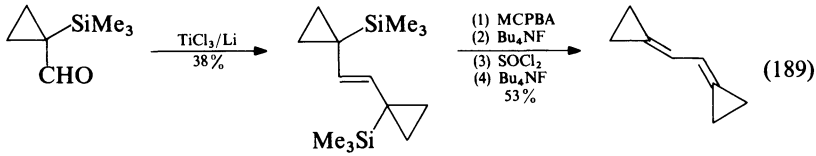
Treatment with potassium hydroxide/methanol and acidic workup will afford an electrophilic methylenecyclopropane derivative[390] which can add nucleophiles or take part in cycloadditions. A tandem Michael addition of this compound with the enolate of an enone approaches the carbon skeleton of the terpene eremophilane (equation 188)[391].



(188)

Most reactions with these chlorinated vinyl-, alkynyl- and methylenecyclopropanes reported so far[21] preserve the cyclopropane unit. Remembering the restrictions set up in the introductory sentence, no more details will therefore be discussed here. Nevertheless, many of the products might participate in important future transformations.

Another novel class of compounds, dicyclopropylideneethanes, has been realized by the Paquette group. The parent compound which was examined in a few cycloaddition reactions, has been synthesized as illustrated in equation 189, passing a biscyclopropylethylene as crucial intermediate[392].

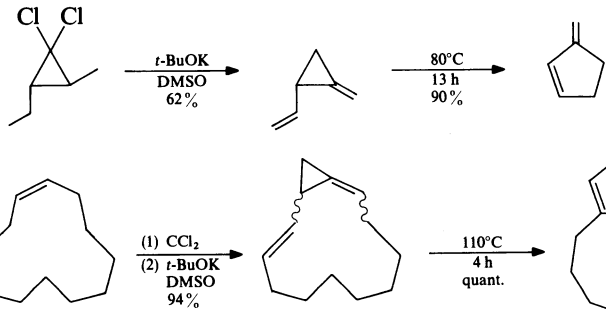


(189)

VIII. METHYLENECYCLOPROPANES

Methylenecyclopropanes have so far not found extensive use in organic synthesis, although reactions reported are promising and the future will certainly show more applications of these highly strained molecules.

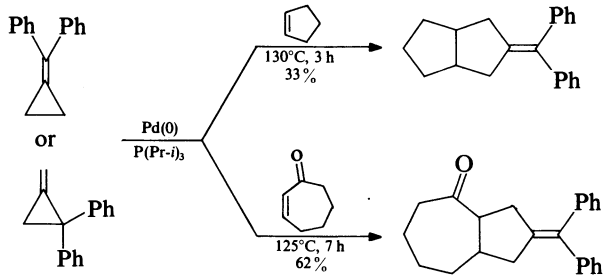
Neglected potential lies in the rearrangement of vinylmethylenecyclopropanes which, as outlined in equation 190, gives methylenecyclopentenes[393, 394]. This process could be extended to bicyclic compounds forming annulated methylenecyclopentenes in certain cases (equation 91)[395].



(190)

(191)

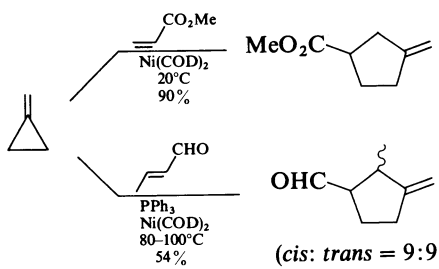
Binger and his students have developed valuable methods for cycloadditions of methylenecyclopropanes to olefins catalysed by Ni(0) or Pd(0). Both electron-rich and electron-deficient alkenes react with diphenylmethylenecyclopropane in the presence of Pd(0) (equation 192). Since the diphenylmethylene unit in the products can be transformed to other groups, a nice way to form functionalized cyclopentanes has thus been established[396].



(192)

cis: *trans* = 6:94

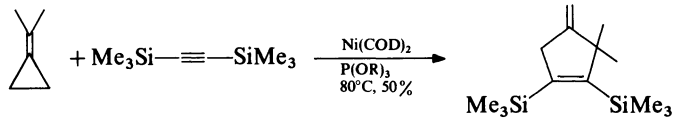
Ni(0) catalysis is able to induce reactions of methylenecyclopropane with olefins activated by electron-withdrawing groups (equation 193)[397]. These cycloadditions work with the utmost efficiency in the case shown, whereas more substituted components might give lower yields due to competing side reactions such as cyclo- and codimerization. These problems could be circumvented by employing new Ni(0) systems with triarylphosphines as cocatalysts[398] (equation 193). Similar conditions lead to the smooth addition of dialkylmethylenecyclopropanes to electron-deficient olefins[399].



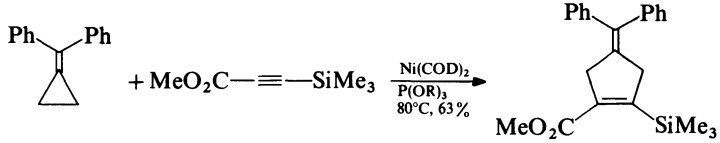
(193)

(*cis*: *trans* = 9:91)

Most importantly, even asymmetric induction with a maximum of 64 % d.e. is achievable by starting with optically active 8-phenylmenthyl acrylate[400]. Recently the Binger group has also reported the cycloadditions to alkynylsilanes forming 4-methylene-1-cyclopentenes (equations 194 and 195)[401]. However, in many examples regiochemical problems concerning methylenecyclopropane as well as alkyne substituents might limit practical application.

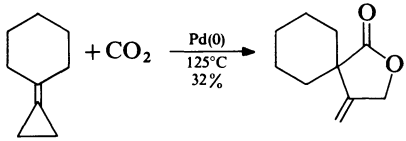


(194)



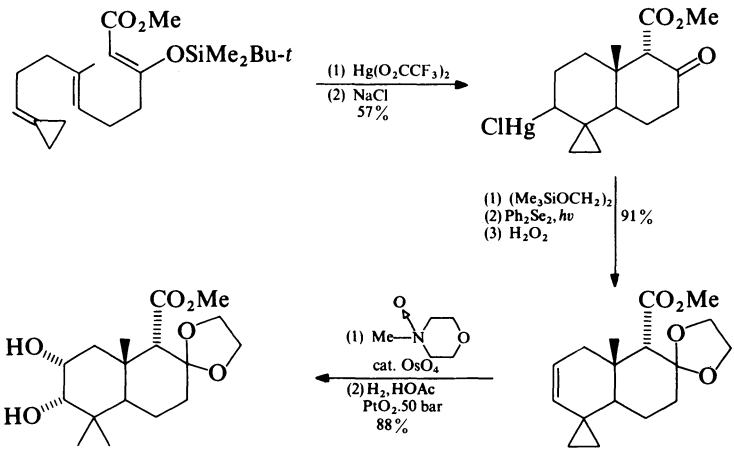
(195)

Early reports of an α-methallylation reaction of cyclohexenones employ Pd(0) and methylenecyclopropane[402], whereas a preparation of several β-methylene γ-butyrolactones adds carbon dioxide under Pd(0) catalysis (equation 196)[403].



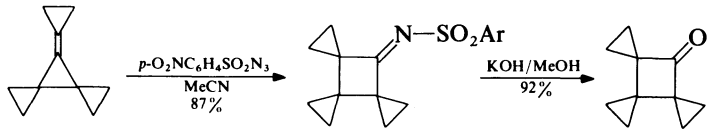
(196)

Surprisingly, additions of electrophiles, radicals, and nucleophiles to methylene cyclopropane have rarely been executed under synthetic conditions. A sequence leading to the complement inhibitor K-76 published recently[404] very smartly takes advantage of a methylenecyclopropane participation in the polyene cyclization shown in equation 197. Hydroxylation of the vinylcyclopropane double bond and hydrogenolysis of the three membered ring are subsequent essential reactions.

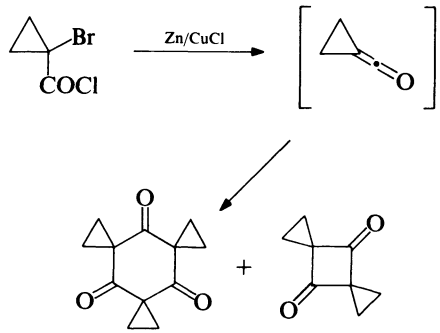


(197)

Addition of *p*-nitrobenzenesulphonyl azide to 7-cycloprophylidene-dispiro[2.0.2.1]heptane leading to a cyclobutanone is a key step in a very nice approach to polyspiranes (equation 198)[405]. A unique ketene is an intermediate in the preparation of the dione and trione displayed in equation 199[406, 407], which might serve as precursors for interesting sterically crowded cyclobutane and cyclohexane derivatives.



(198)



(199)

The future will demonstrate whether cleavage reactions of alkenylidenecyclopropanes employing acidic or reductive conditions[408] are synthetically useful.

IX. CONCLUDING REMARKS

The sections above demonstrate that many transformations which are not easily achieved by other routes can be performed by using the cyclopropyl group as a tool for synthetic purposes. Very often these methods can be classified as reactions with umpolung and are therefore of special importance for synthetic strategy.

Although most of the thinkable principal substituents able to activate the cyclopropane core had been examined by the time this review was written, not all possible combinations of these functional groups had been tested. Yet multiactivated cyclopropanes should be a rewarding field displaying a particularly rich and useful chemistry as has been indicated by the behaviour of donor–acceptor-substituted cyclopropanes. These multiactivated cyclopropanes as well as free radical reactions and transition metal-induced processes deserve to attract more attention in future.

Owing to the stereospecificity of many preparation methods for cyclopropanes and the possibility of controlling stereochemistry at the rigid three-membered ring system by successive manipulations, many cyclopropane derivatives are accessible with a high degree of diastereoselectivity. So far, the challenge in the translation of this defined stereochemistry to the ring-opened products has not very often been taken up. This should be a field of future activity with interest from both a mechanistic and a synthetic point of view. Finally, asymmetric synthesis might be achievable by application of cyclopropanes in a way both efficient and elegant, since several cyclopropane syntheses employing optically active *catalysts* result in enantiomeric excess of up to 100%. These enantiomerically enriched or

pure cyclopropanes just await cleavage reactions which can be expected to render a new dimension to the synthetic use of cyclopropanes.

X. ACKNOWLEDGEMENTS

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CHAPTER **9**

Synthesis and reactivity of electrophilic cyclopropanes

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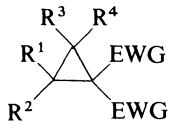
I. INTRODUCTION

Although the first electrophilic cyclopropane, diethyl cyclopropane-1,1-dicarboxylate (EWG = COOEt; $R^1 = R^2 = R^3 = R^4 = H$), was prepared a century ago in 1885 by Perkin[1] the chemistry of electrophilic cyclopropanes geminally substituted with two electron-withdrawing groups (EWG) started to be explored only fifty years later. From that moment the synthesis and the investigation of the chemical properties of cyclopropanes substituted with one electron-withdrawing group EWG (monoactivated) and with two EWGs (diactivated) has been expanded rapidly and continuously mainly on account of their applications in the field of the insecticidal synthetic pyrethroids. It should be mentioned that in several reports the term 'electrophilic cyclopropane' is not limited to cyclopropanes, geminally substituted with two EWGs (*sensu strictu*), but also to



EWG: COOR, COR, CN, SO_2R, $P(O)(OR)_2$, NO_2

cyclopropanes bearing one EWG. The chemistry of the cyclopropane ring is well documented[2-6] but no comprehensive review appeared hitherto dealing with the synthesis and reactivity of electrophilic cyclopropanes (*sensu strictu*). Only one excellent review concerning the use of electrophilic cyclopropanes in organic synthesis has been published by Danishefsky in 1979[7].

This chapter will deal mainly with the synthesis and reactivity of electrophilic cyclopropanes and only these procedures and reactions will be investigated which give rise to cyclopropanes geminally substituted with two EWGs. Nevertheless, the preparation of monoactivated cyclopropanes will be mentioned to some extent because a number of procedures for the synthesis of electrophilic cyclopropanes have been developed for cyclopropanes bearing one EWG. Therefore, the synthesis and reactivity of the latter compounds cannot be excluded, due to the close relationship and the numerous studies concerning reaction mechanisms for these compounds.

Also functional group transformations of electrophilic cyclopropanes yielding other electrophilic cyclopropanes will not be the subject of this chapter.

This review covers the literature on electrophilic cyclopropanes up to the end of 1984.

II. SYNTHESIS OF ELECTROPHILIC CYCLOPROPANES

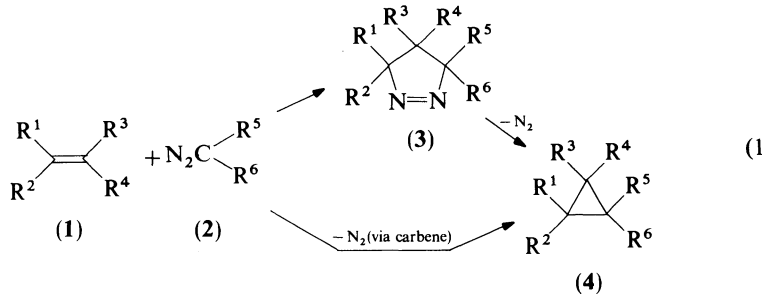
During the last decade two reviews dealing with the synthesis of functionalized cyclopropanes have been published[4,5]. Mainly cyclopropanes substituted with one electron-withdrawing group were treated and no systematic investigation of electrophilic cyclopropanes geminally substituted with two electron-withdrawing groups was described.

In this chapter the general methods leading to these electrophilic cyclopropanes will be described and the procedures are classified according to the reaction type and not to the substrates and/or reagents. Some mechanistic interpretations of the results will be treated in some important cases.

A. Cyclopropanation via Addition Reactions

1. Cyclopropanation via diazo syntheses and addition of carbenoïds

One of the most widely used procedures for the synthesis of electrophilic cyclopropanes consists of the reaction of olefins with diazo compounds. The electron-withdrawing group (EWG) can either be situated in the olefin or in the diazo compound or in both reactants. Diazoalkanes are expected to undergo a 1,3-dipolar cycloaddition reaction with activated olefins resulting in the formation of pyrazolines which upon expulsion of nitrogen give rise to cyclopropanes. In addition carbenes can be generated under various conditions (among others from diazoalkanes) and reaction with olefins affords the corresponding electrophilic cyclopropanes (equation 1).



(1)

Numerous examples of these two types of reaction are encountered in the field of the insecticidal pyrethroids[4,5].

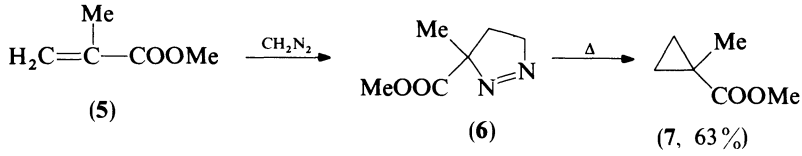
a. Synthesis of electrophilic cyclopropanes via 1,3-dipolar cycloaddition reactions of diazoalkanes with olefinic substrates·

Addition reactions of diazoalkanes, especially diazomethane, diazopropane, diphenyldiazomethane and ethyl diazoacetate, onto olefins, substituted with one or two electron-withdrawing groups take place very smoothly affording pyrazolines which upon heating or photolysis can give rise to the corresponding substituted cyclopropanes by elimination of nitrogen.

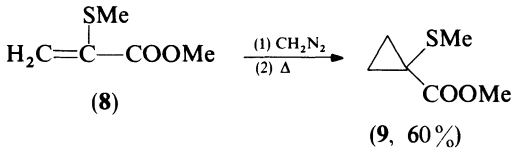
As olefinic substrates α,β-unsaturated carbonyl compounds (esters, anhydrides, ketones, quinones), nitriles and nitro compounds can be used. The rate of addition of the diazo compounds is dependent upon the nature of the diazo compound and generally the following order of reactivity can be observed: diazomethane > diphenyldiazomethane > methyl diazoacetate > diazoketones.

The reaction is usually carried out by reacting both components (diazoalkane and olefin) in an etheral solution for several days. The reaction time must be prolonged when highly substituted olefins are used and, in these cases, the yields are not higher than 75% in general[8].

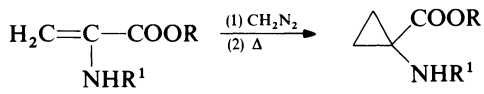
For example methyl 1-methylcyclopropanecarboxylate (7) can be prepared by treatment of methyl methacrylate (5) with diazomethane in a 63% yield (equation 2)[9]. Also acrylates



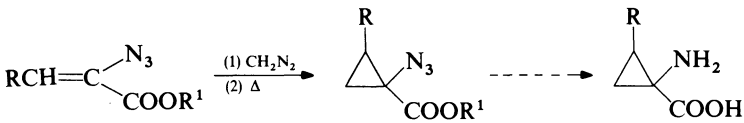
(5) (6) (7, 63%)



(8) (9, 60%)

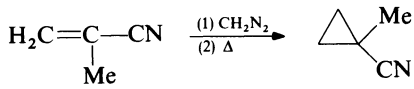


(10) (11, 60–78%) (2)

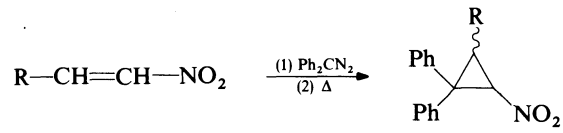


(12) (13) (14)

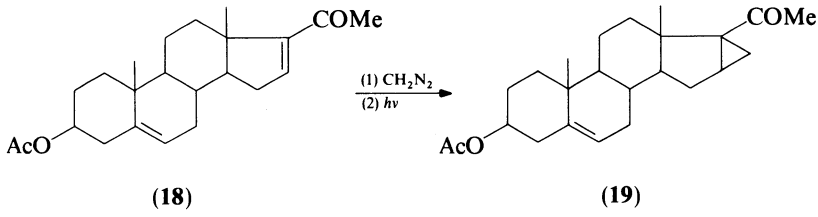
substituted in the α-position with various functionalities (e.g. **8**, **10**, **12**) easily undergo cyclopropanation yielding geminally substituted cyclopropanecarboxylates, e.g. alkylthio (**9**)[10], phenylamino (**11**, R^1 = Ph)[11,12] and azido (**13**) derivatives[13]. In addition cyclopropane-1,2-dicarboxylates[14] and cyclopropane-1,2,3-tricarboxylates[15] were prepared by a similar procedure in which fumarates are treated with diazomethane and diazoacetates respectively. Not only acrylates but also α,β-unsaturated nitriles[16], nitro-olefins (e.g. **16**)[17], enones (e.g. **18**)[18] and α,β-unsaturated phosphonates (e.g. **20**)[19]



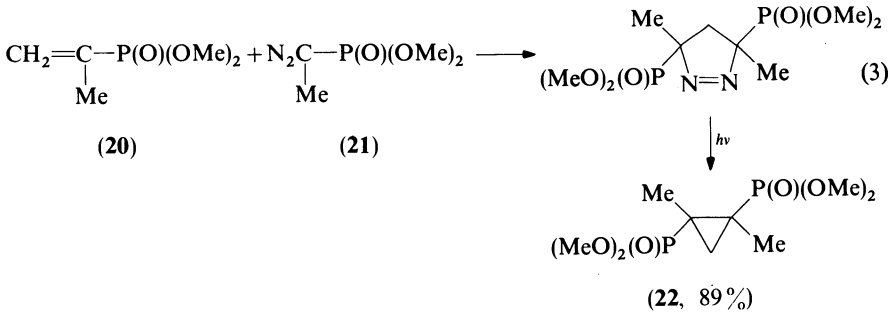
(**15**, 55%)



(**16**) (**17**, 36–67%)



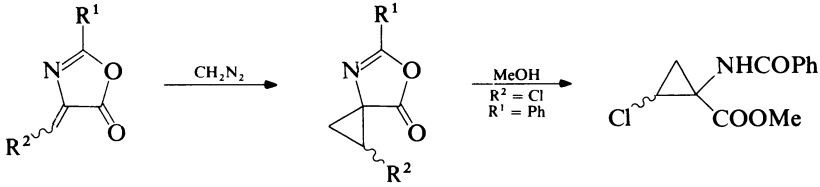
(18) (19)



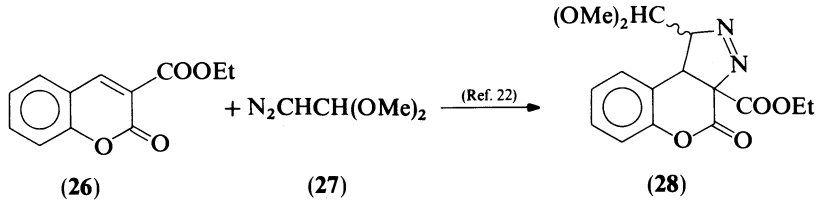
(20) (21) (3)

(22, 89%)

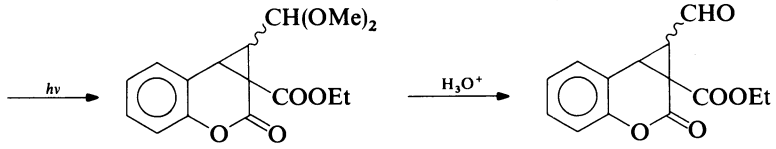
are apt to undergo cyclopropanation giving the cyclopropanes **15**, **17**, **19** and **22**, respectively (equation 3). Several heterocyclic compounds have been the subject of cyclopropanation by reaction with diazoalkanes as exemplified by the reactions shown in equations 4–7. Cyclopropanation of the *exo* olefinic double bond of **23** with diazomethane



(23) (24) (25, 55%) (4)

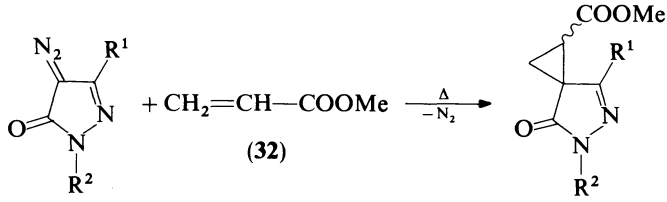


(26) (27) (28) (5)



(29) (30, 56%)

provides access to spiro compounds **24**, which are useful precursors to functionalized 1-aminocyclopropanecarboxylic acid derivatives **25** (equation 4)[20,21]. Recently 1,3-di-substituted diazopyrazolinones (**31**) are found to enter cycloaddition with methyl acrylate to give spirocyclopropanes (**33**) (equation 6)[23]. The ratio between the *cis* and *trans*

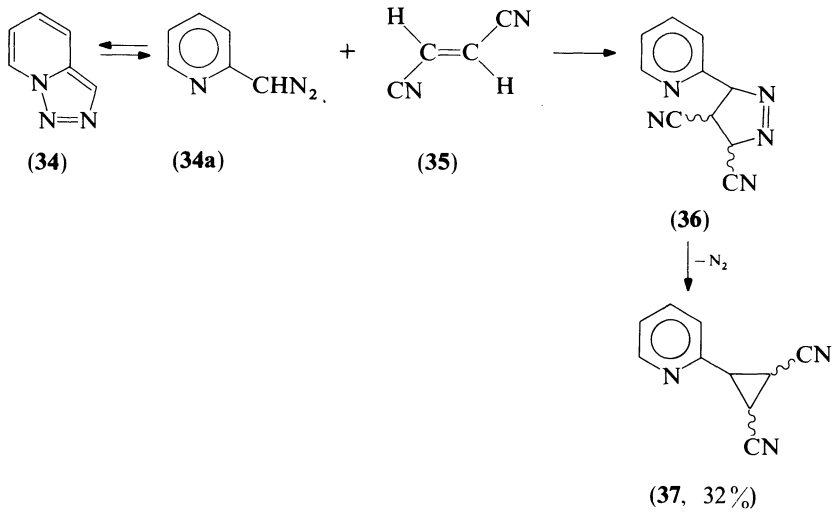


(6)

(**31**) (**32**)

(**33**, $R^1 = R^2$ = Ph: 83%)

stereoisomers seems to be strongly dependent upon the nature of R^1 (alkyl or aryl functions). 2-(Diazomethyl)pyridine (**34a**), a valence tautomer of 1,2,3-triazolo[1,5-a]pyridine (**34**), can be trapped by fumaronitrile (**35**), leading to 3-(2-pyridyl)-1,2-cyclopropanedicarbonitrile (**37**) via decomposition of a 1-pyrazoline derivative (**36**) (equation 7)[24]. In contrast to the preparation of cyclopropanes substituted with one EWG,

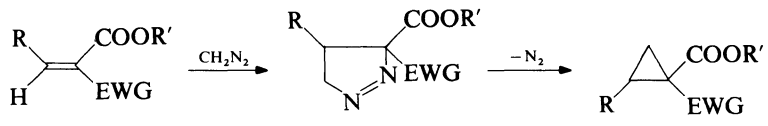


(**34**) (**34a**) (**35**) (**36**)

(7)

(**37**, 32%)

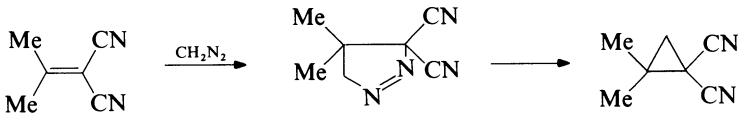
the 1,3-dipolar cycloaddition of diazo compounds onto olefins geminally substituted with two EWGs (**38**) is not widely used for the synthesis of electrophilic cyclopropanes because the formation of these cyclopropanes is accompanied by the presence of side-products



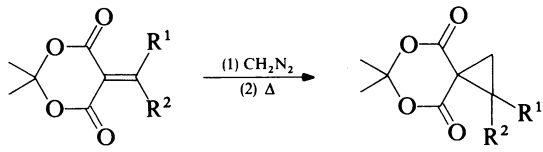
(**38**) (**39**) (**40**, 25–85%)

EWG: COOR′, COMe, CN

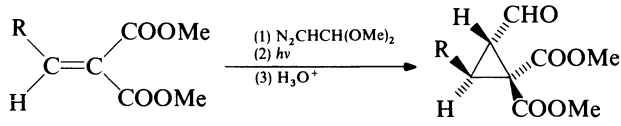
Refs 25–27



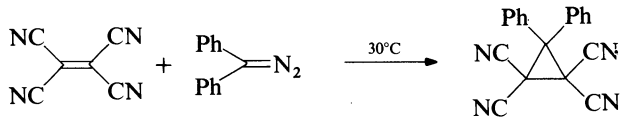
(41) (42) (43, 32%) Ref. 28



(44) (45, 12–60%) Ref. 29

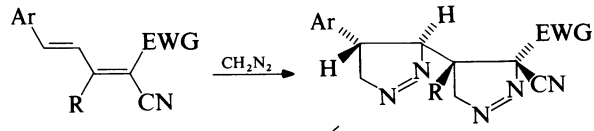


(46) (47, > 80%) Ref. 30

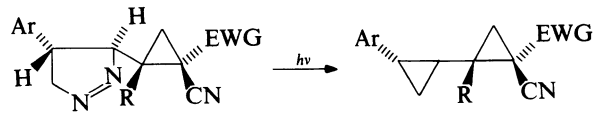


(48) (49, 91%) Ref. 31

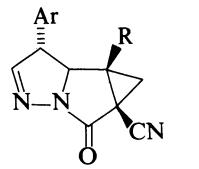
(8)



(50) (51)



(52) (53)

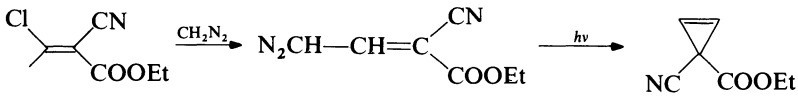


(54)

formed during the thermolysis or photolysis of the intermediate pyrazolines. Nevertheless several electrophilic cyclopropanes have been prepared following this procedure as illustrated in the examples given in equation 8.

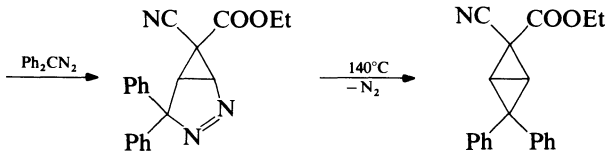
Double addition of diazomethane to cinnamylidene cyanoacetic ester **50** (EWG = COOR') and corresponding dinitriles (**51**) (EWG = CN) followed by thermolysis gave rise to pyrazoline-substituted cyclopropanes (**52**) which upon photolysis and acid treatment afforded biscyclopropanes (**53**) and tricyclic compounds (**54**) respectively[32].

The electrophilic cyclopropane **59** is prepared according to a reaction scheme which involved the photolysis of ethyl diazoethylidenecyanoacetate (**56**) to give the cyclopropene (**57**) derivative which in turn on addition of diphenyldiazomethane afforded the bicyclic pyrazoline (**58**). Thermolysis of **58** produced bicyclo[1.1.0]butane derivative **59** (equation 9)[33].



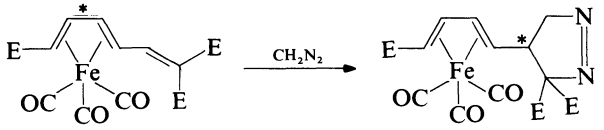
(**55**) (**56**) (**57**)

(9)



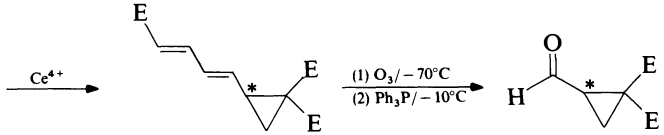
(**58**) (**59**, 70%)

Chiral electrophilic cyclopropanes (**63**) are prepared in high enantiomeric excess starting from butadiene–iron tricarbonyl complexes (**60**) containing a non-complexed double bond. Reaction with diazomethane and decomposition of the resulting pyrazolines (**61**) in the presence of Ce^{4+} gave the corresponding chiral cyclopropanes (**62**). Breakdown of the dienic substituent of electrophilic cyclopropane (**62**) by means of ozonization resulted in the formation of formyl-substituted electrophilic cyclopropane (**63**) still carrying the asymmetric centre (equation 10)[34,35].



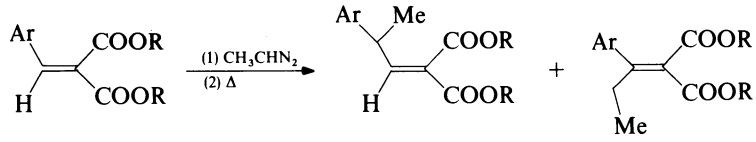
(**60**) (**61**)

(10)

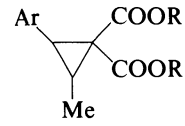


E = COOMe (**62**) (**63**)

It should be pointed out that in most cases the formation of the electrophilic cyclopropanes **67** is accompanied by the generation of isomeric olefinic compounds **65** and **66** (equation 11)[26]. Reactions of 1,1-disubstituted olefins (**38**) which carry cyano,



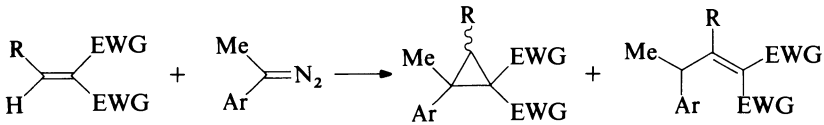
(**64**) (**65**, 70%) (**66**, 18%) (11)



(**67**, 12%) Ref. 26

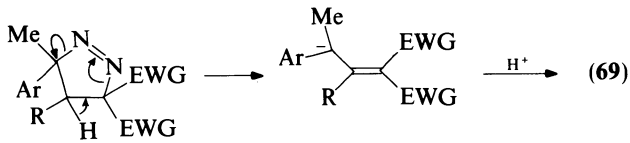
alkoxycarbonyl, or halogen as a substituent with methylaryldiazomethanes in dichloromethane produce 1,1-disubstituted 3-aryl-1-butenes (**69**) and 1,1-disubstituted 2-methyl-2-arylcyclopropanes (**68**). Product ratios seem to be dependent upon the substituents of the olefin. In the case of an olefin with both cyano and alkoxycarbonyl groups, acyclic products are more favourable. When using an olefinic substrate with both either a cyano or alkoxycarbonyl group and either a halogen or hydrogen, cyclopropanes are more selectively produced.

The product ratio is also dependent upon the aryl substituents[36]. The reaction products are formed via the mechanisms depicted in equation 12.

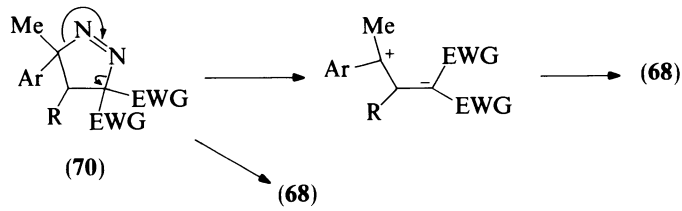


(**38**) (**68**) (**69**)

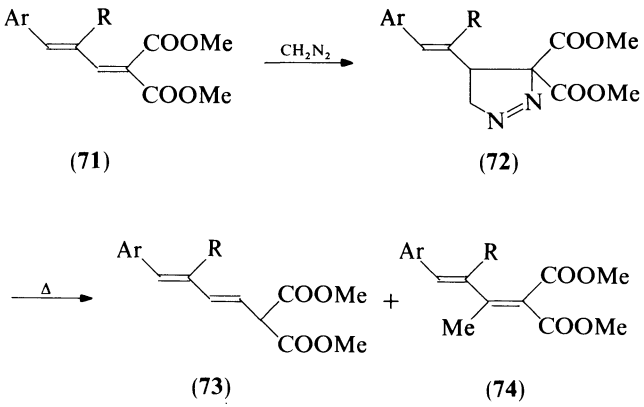
EWG: COOR′, CN, Cl, Br



(**70**) (12)



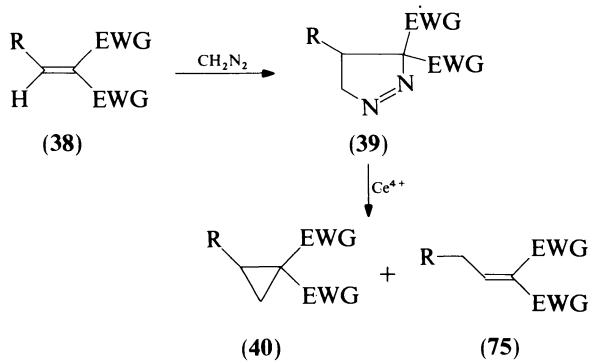
In some cases the decomposition of the intermediate pyrazolines, e.g. **72**, resulted only in the formation of the acyclic compounds **73** and **74** (equation 13)[37]. Electrophilic



(71) (72) (13)

(73) (74)

cyclopropanes are also conveniently prepared by decomposition of the corresponding pyrazolines in the presence of a small amount of $Ce(NH_4)_2(NO_3)_6$. In some cases the reaction is accompanied by methylene insertion (equation 14)[38]. The mechanism involves

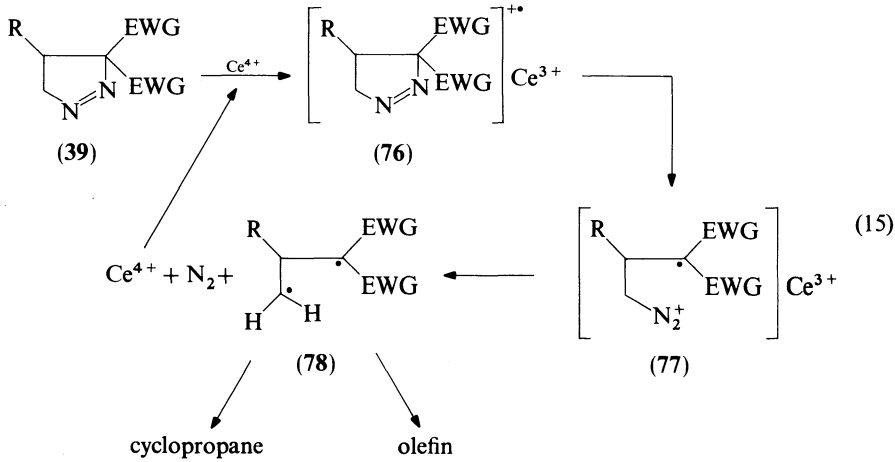


(38) (39) (14)

(40) (75)

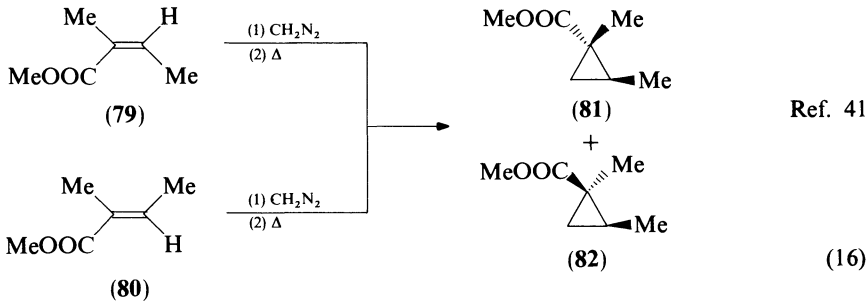
an oxidation of the pyrazoline **39** by Ce^{4+} to give a radical cation (**76**) which undergoes bond cleavage to furnish a diazonium radical (**77**). In the presence of Ce^{3+}, **77** gives back Ce^{4+} together with the diradical **78**. Depending upon the nature of R, a rearrangement occurs to provide either a cyclopropane or an olefin (equation 15)[38]. The mechanisms involved in the formation of electrophilic cyclopropanes have been the subject of several studies. While for the first step, a 1,3-dipolar cycloaddition, the mechanism is fully understood[39], the decomposition of the resulting pyrazoline derivatives is not entirely understood due to the lack of stereospecificity, and the formation of acyclic compounds.

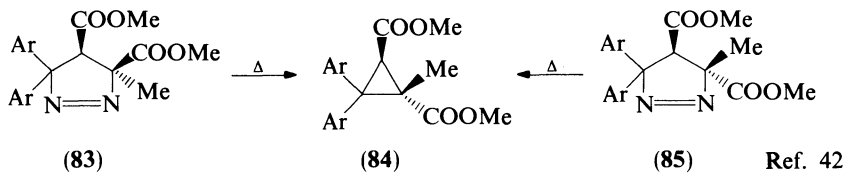
The stereochemical outcome of the pyrazoline decomposition can be varied according to the substrate and the reaction conditions. Although retention predominates, inversion



(15)

or lack of stereospecificity has been observed, as shown in equation 16[40]. The decomposition of 1-pyrazolines to give cyclopropanes could in principle follow two different pathways: one involving a dipolar transition state and one involving diradical

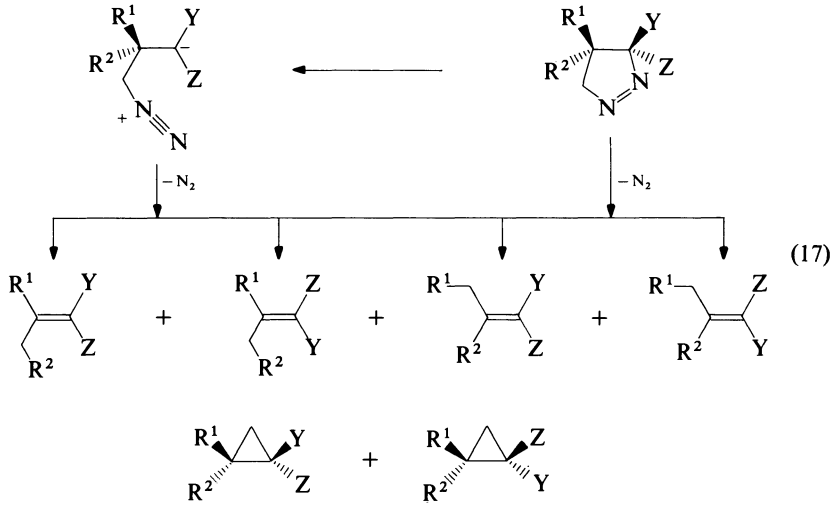




intermediates. The former is usually expected when the ring contains charge-stabilizing substituents and the latter pathway is preferred with unsubstituted or alkyl-substituted 1-pyrazolines and when the decomposition of the pyrazolines is photochemically performed[43,44].

The thermolysis of 1-pyrazolines containing electron-withdrawing groups in position 3 has been thoroughly investigated with reference to product distribution and kinetic parameters[45]. The results point to a two-step mechanism in protic solvents by ring-opening via the N(2)–C(3) bond and the resulting partial negative charge is then stabilized

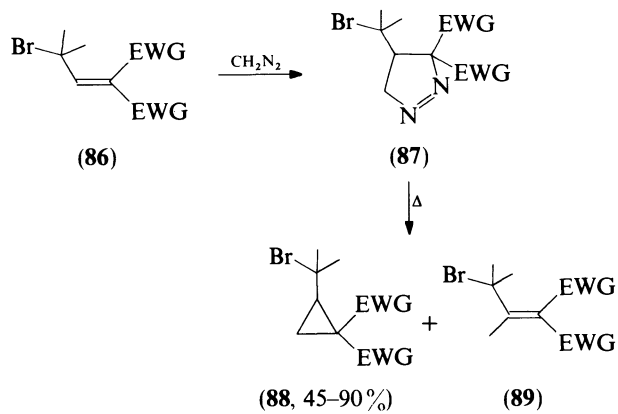
by the EWGs at the C(4) position. However steric effects can lead to the preference of a one-step process (equation 17).



(17)

Y, Z = EWG

Copper salts accelerate the decomposition and completely reverse the product distribution in favour of the cyclopropane derivatives. The solvent also seems to be of great importance in determining the product distribution. The ratio olefin–cyclopropane is increased by using solvents with higher dielectric constants[46]. This phenomenon is illustrated by the decomposition of 4-(1-bromo-1-methylethyl)pyrazolines (**87**)[47–49]. In non-polar solvents both a cyclopropane (**88**) and an olefinic product (**89**) are formed (equation 18). In polar solvents, both protic and aprotic, the cyclopropane **88** is the only product observed. The rate of formation of **88** is very solvent dependent. A striking feature is a very strong acceleration rate in the cyclopropane formation with increasing solvent

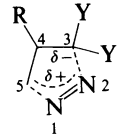


(18)

EWG: COOMe, CN

polarity (5500 times faster in ethanol than in benzene), an observation pointing to a transition state more polar than the ground state.

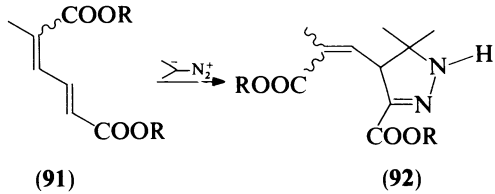
This large solvent effect points to a polarized transition state. In accordance with the fact that the stereochemistry is retained in the cyclopropane formation, it is assumed that the N(2)–C(3) bond is not completely broken before bonding between C(3) and C(5) has started, and a transition state like **90** is proposed[47–49]. The effect of having a bromine



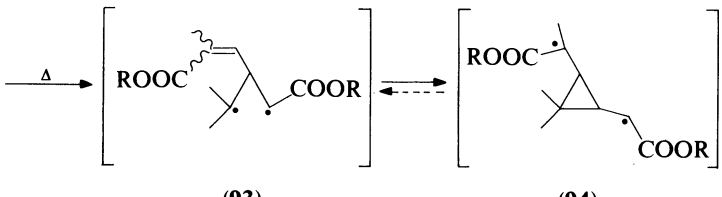
(90)

atom in the side chain in the 4-position is rather dramatic. The rate of decomposition is about 50-fold higher than that of the non-brominated analogue. This accelerated decomposition rate is reflected in a 325-fold rate increase in cyclopropane formation and an 8-fold rate decrease in alkene formation.

A biradical intermediate in the decomposition of the pyrazoline derivative (**92**) via thermolysis and photolysis has been postulated (equation 19)[50]. The diradical **93** can react



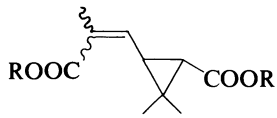
(91) **(92)**

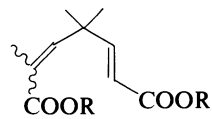


(19)

(93) **(94)**

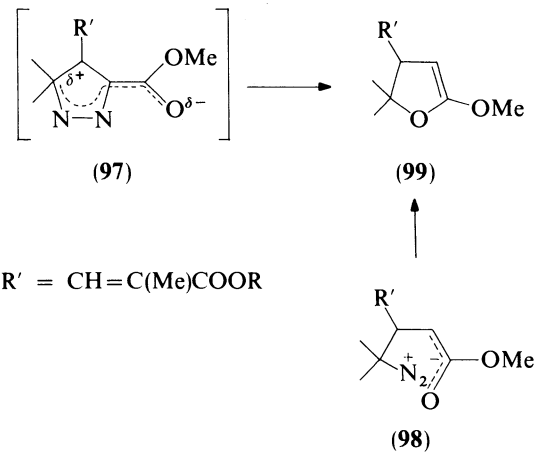
vinylcyclopropane system di-π-methane system





(95, R = Me: 28%) **(96)**

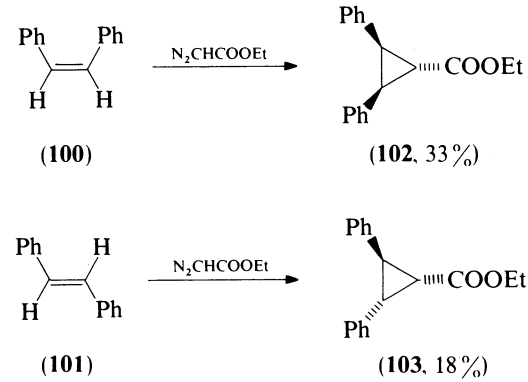
further via two routes: either by stereospecific ring-closure into vinylcyclopropane derivatives (**95**) or by rearrangement via **94** into the di-π-methane derivatives (**96**). During the reaction the formation of 2,3-dihydrofuran derivatives (**99**) is observed. The latter compounds can be formed via a polar transition state (**97**) or via a dipolar intermediate (**98**) (equation 20).



(**97**) (**99**) (**98**) (20)

b. Synthesis of electrophilic cyclopropanes via addition of carbenoids

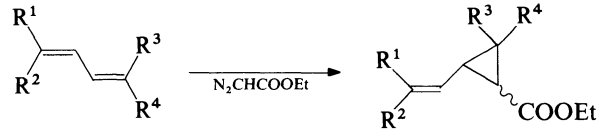
The addition of carbenes to suitable olefins is one of the most general procedures for synthesizing cyclopropanes substituted with electron-withdrawing functions. Ethyl 2-phenylcyclopropanecarboxylate was first prepared by the action of ethyl diazoacetate (EDA) on styrene[51]. Due to the concerted nature of the addition the reaction is stereospecific. Reaction of *cis*- (**100**) and *trans*- (**101**) stilbene with ethyl diazoacetate gave the *cis*- and *trans*-ethyl 2,3-diphenylcyclopropanecarboxylates **102** and **103** respectively (equation 21)[52]. This type of reaction can be performed with or without the presence of a



(**100**) (**102**, 33%) (21)

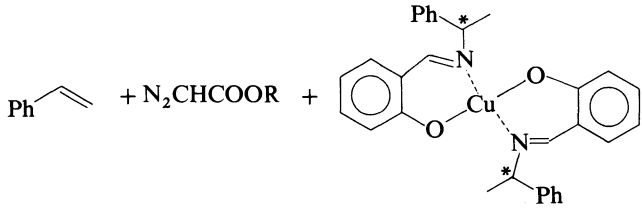
(**101**) (**103**, 18%)

catalyst. Homogeneous as well as heterogeneous catalytic reaction conditions can be utilized. The influence of these different reaction conditions on the yield is illustrated by the reaction of dienes (**104**) with ethyl diazoacetate (equation 22). Without any catalyst the



(104) (105, 28–98%) (22)

yield of cyclopropanes (**105**) is low[53], but the presence of copper-bronze raises the yield considerably[54]. However, performing the reaction in the presence of rhodium(II)acetate gives still better yields[55]. Copper and copper salts are used as heterogeneous catalyst[56] next to Cu complexes with carbenes[57]. The preparation of cyclopropanes **107** and **108** is an example of a copper-catalysed carbene reaction using an optically active Cu complex (**106**) (equation 23)[58]. Copper complexes with Schiff base ligands have been used for optical

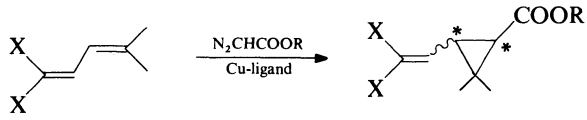


(106) (23)

(107) (108)

(72%: *cis* + *trans*)

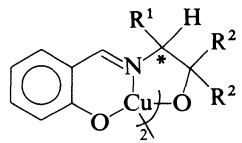
induction (up to 65.5%) in the formation of 2,2-diphenylcyclopropanecarboxylic acids[59] and pyrethroid derivatives (**110**) (equation 24)[60]. The Cu-catalysed transformation of



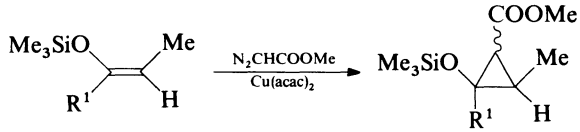
(109) (110)

X = halogen (24)

Cu-ligand:



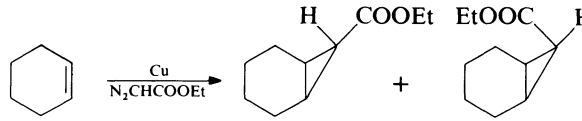
diazoacetates with olefins gave rise to a stereospecific *cis*-addition in favour of the least sterically hindered isomer as illustrated in equation 25[61].



(25)

(**110a**, 45–89%)

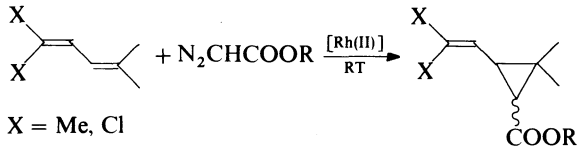
Cyclopropanation of cycloalkenes by this procedure also produced the least sterically hindered bicyclic compound. For example, the copper-catalysed addition of ethyl diazoacetate onto cyclohexene afforded 69% of the *exo* (**111**) and 4% of the *endo* compound (**111a**) (equation 26)[62]. Next to the traditional Cu catalysts, homogeneous



(26)

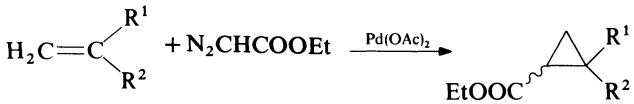
(**111**, 69%) (**111a**, 4%)

catalysis by transition metal complexes was shown to be very efficient in reactions whereby a carbene is transferred onto an olefinic double bond as illustrated by the reactions in equation 27.



X = Me, Cl

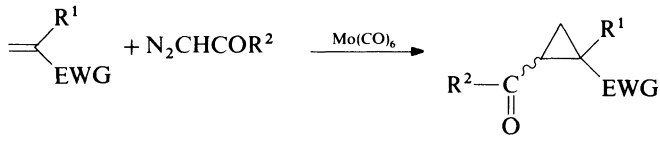
(**110b**, 54–98%) Ref. 63



(**112**, 64–85%) Ref. 64

R^1: H, alkyl
R^2 : COOR, COMe

(27)

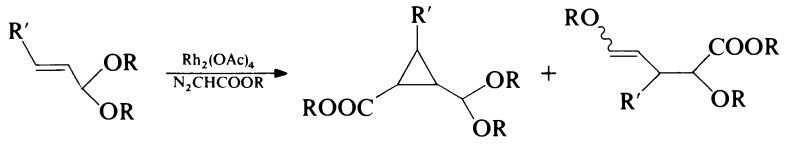


R^2 = Ph, OR
EWG = electron-withdrawing group

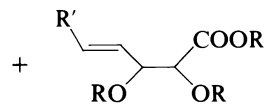
(**113**, 25–79%) Ref. 65

Rhodium(II) carboxylates and carbonyls offer a number of advantages over copper[63]. Palladium[64], molybdenum complexes[65] and chiral cobalt complexes[409] are also often

used in cyclopropanation reactions. Rhodium essentially promotes a carbenoïd mechanism involving an electrophilic attack of uncomplexed olefins, while a substantial olefin coordination is observed with palladium. By comparison, the classical copper derivatives are essentially borderline cases: most often they behave as carbenoïd catalysts, except when associated with very weak ligands such as in copper triflate. It should be pointed out that in the absence of catalysts 1-pyrazolines are formed by 1,3-dipolar cycloaddition, and cyclopropane formation is insignificant under reaction conditions identical with those employed in catalytic reactions. Nevertheless byproducts can be formed during the cyclopropanation of olefins. One of the most encountered side-reactions is dimerization of the carbenoid with formation of fumarates and maleates and alkoxyacetates, but their yield is dependent on the rate of addition of the diazoacetates. Other byproducts resulted from rearrangements of intermediate ylides as illustrated by the reaction of allylic acetals (**114**) with an alkyl diazoacetate in the presence of rhodium(II) acetate (equation 28)[66].

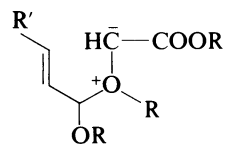


(**114**) (**115**) (**116**) (28)



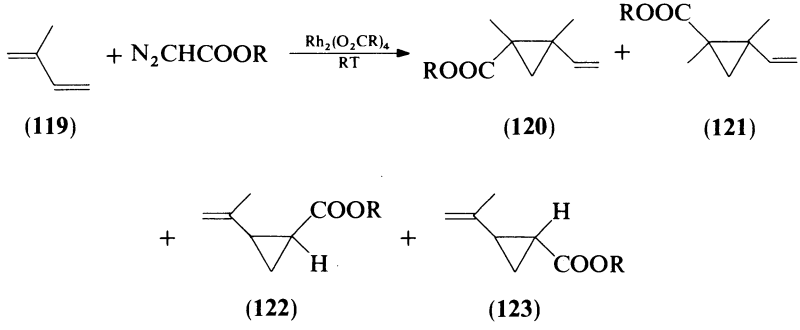
(**117**)

Compounds **116** originated from a 2,3-sigmatropic rearrangement of the oxygen ylide **118**, while compounds **117** are formed by a 1,2-insertion reaction. No cyclopropanation took place with analogous thioacetals. The carboxylate counter-ion in the rhodium(II)



(**118**)

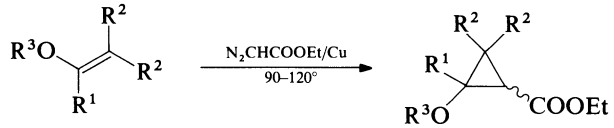
carboxylates $Rh_2(O_2CR')_4$ plays an important role. According to its electronic, steric and/or lipophilic requirements, it largely determines the efficiency and selectivity of carbenoid intermediates (regio-and stereo selectivities) as shown in the cyclopropanation of isoprene (**119**) which occurs preferentially (> 60%) at the more electron-rich double bond to give mainly **120** and **121** (equation 29)[67]. Cyclopropanation with diazoacetates can also be carried out photochemically but the yields of cyclic products are usually lower than in the catalysed reactions due to the formation of acyclic compounds[62, 68].



(119) (120) (121) (122) (123)

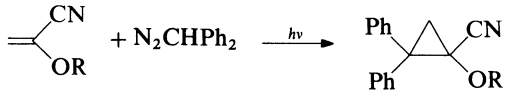
(29)

In general it has been postulated that the substitution of an electron-donating group enhances the olefin reactivity toward carbenes and that substitution by electron-withdrawing groups reduces this reactivity (equation 30)[69], for instance enol ethers (**124**)



(124) (125, 84–95%) Ref. 70

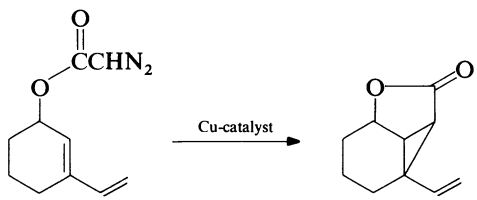
(30)



(126) (127, R = COMe: 70%) Ref. 68

were transformed into 2-alkoxycyclopropane carboxylic esters (**125**) by reaction with ethyl diazoacetate under Cu catalysis[70]. Interestingly, it has been reported that the presence of both an electron-donating and an electron-withdrawing group on the same olefinic carbon as in **126** (equation 30) enhances the carbene addition reactions[68].

Cyclopropanation of olefins with diazoesters can be performed intramolecularly[66] as in the formation of a cyclopropyllactone (**129**) from a cyclohexenyl diazoester in the presence of bis-(*N*-*t*-butylsalicylaldiminato) copper(II) (equation 31)[71]. Next to diazoesters other

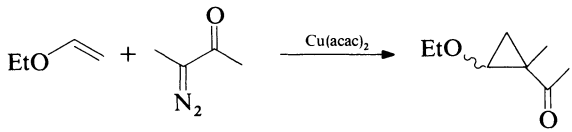


(128) (129, 92%)

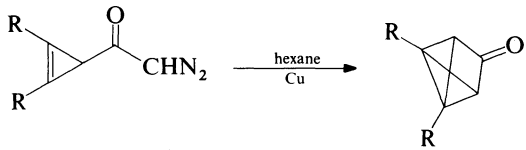
(31)

diazo compounds such as α-diazoketones (**130** and **132**)[72,73], α-diazonitriles (**134**)[74], α-diazopyruvates (**136**)[75] and α-diazosulphones (**138**)[76] have been used in the synthesis of

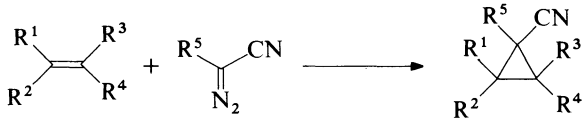
cyclopropanes substituted with electron-withdrawing substituents (equation 32). In addition to the usually expected cyclopropanes, photolytically or thermally generated α-ketocarbenes, heterocyclic compounds such as lactones[77] and furan derivatives[78,389] occasionally appear, mainly as the result of formal 1,3- and 1,4-dipolar cycloadditions.



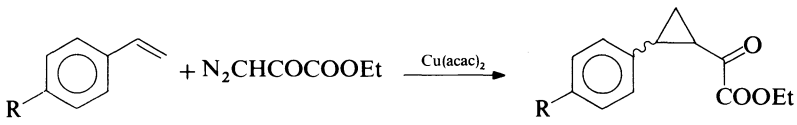
(124) (130) (131, 45%)



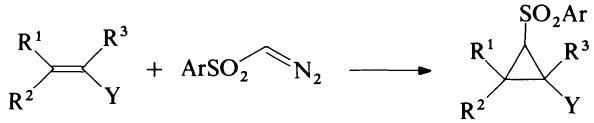
(132) (133) Ref. 73



(134) (135) (32)

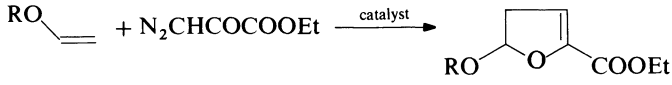


(136) (137, 31–33%)



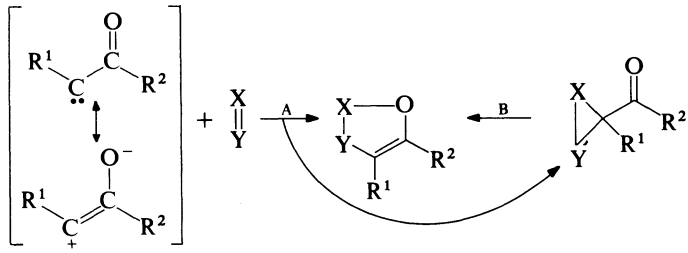
(138) (139)

Thermolysis of ethyl diazopyruvate (**136**) in the presence of enol ethers and bis(acetylacetonato) copper(II) catalyst did not lead to cyclopropane formation but instead a dihydrofuran (**140**) was generated (equation 33)[80].



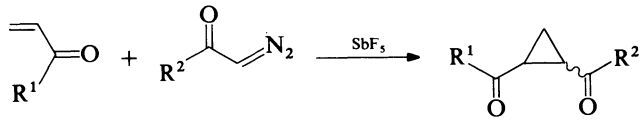
(124) (136) (140, 36–79%) (33)

While 1,4-additions suggest that the oxocarbene reacts as in a cyclopropanation, the 1,3-additions have been conceived as the consequence of the α-oxocarbene acting as a 1,3-dipole (equation 34, route A). Alternatively, the five-membered heterocycles may result from the 1,3-sigmatropic rearrangement of initially formed cyclopropyl ketones in the reaction medium (equation 34, route B).



(34)

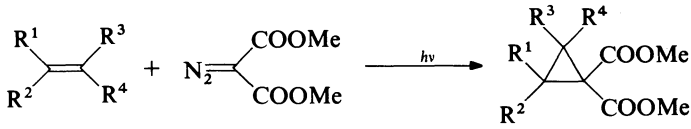
Lewis acid-promoted cyclopropanation of α,β-unsaturated carbonyl compounds by α-diazoketones has been reported to yield 1,2-diacylcyclopropanes of high isomeric purity. Isomerization of these derivatives by antimony pentafluoride produced the more stable geometrical isomer **141** (equation 35)[79].



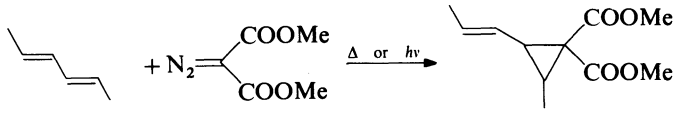
(35)

(**141**, 11–80%)

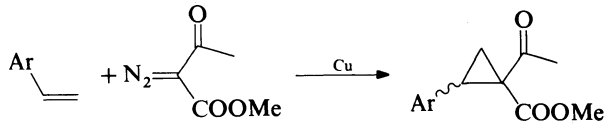
A large number of cyclopropanes geminally substituted with two electron-withdrawing groups have been synthesized by cyclopropanation of olefins with carbenes substituted with two electron-withdrawing groups (equation 36)[81–91]. Spiro-activated cyclopropanes



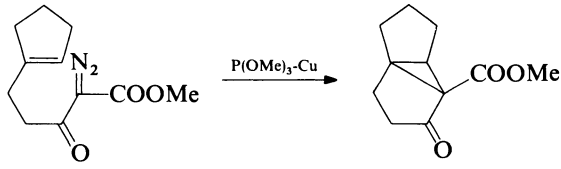
(**142**) (**143**, 50–90%) Refs 81–84



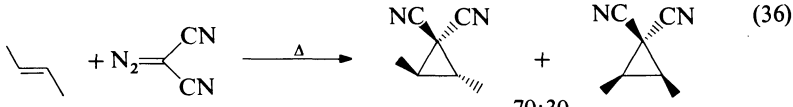
(**142**) (**144**, 44%) Ref. 85



(**145**) (**146**, 31–33%) Ref. 86

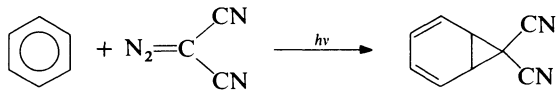


(147) (148, 55%) Refs 87–89



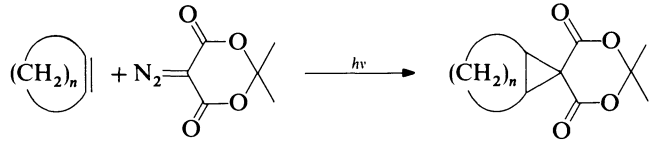
(36)

(149) (150) (151) Ref. 90



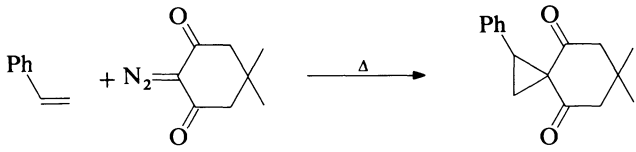
(149) (152, 55%) Ref. 91

154, 156 are synthesized from alkenes via the irradiation of isopropylidene diazomalonate (**153**)[92] and 2-diazodimedone (**155**) (equation 37)[93]. It is worth noting that copper



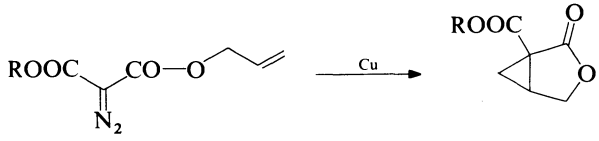
(153) (154, 40–87%)

(37)

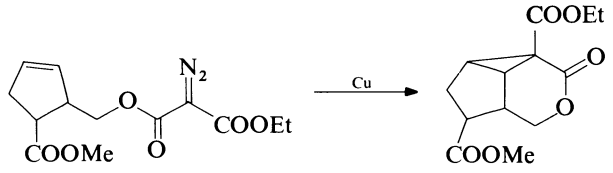


(155) (156, 54%)

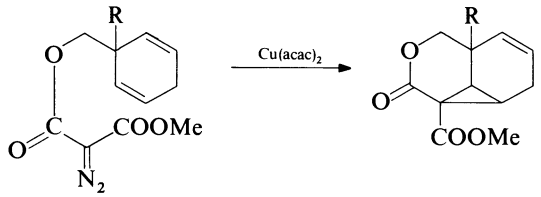
complexes of 3-trifluoroacetyl-(+)-camphor give high optical yields when used as catalysts for the asymmetric cyclopropanation of styrene with diazodimedone[93]. In addition, diazoalkenyl esters are transformed into electrophilic cyclopropanes via an intramolecular cyclopropanation (equation 38)[98].



(157) (158, 50–90%) Ref. 94

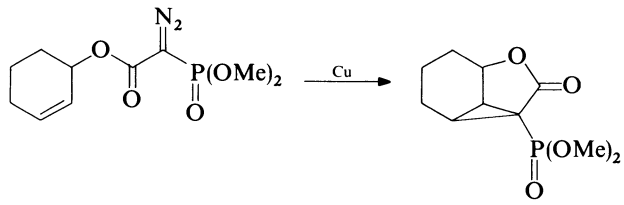


(159) (160, 35%) Ref. 95



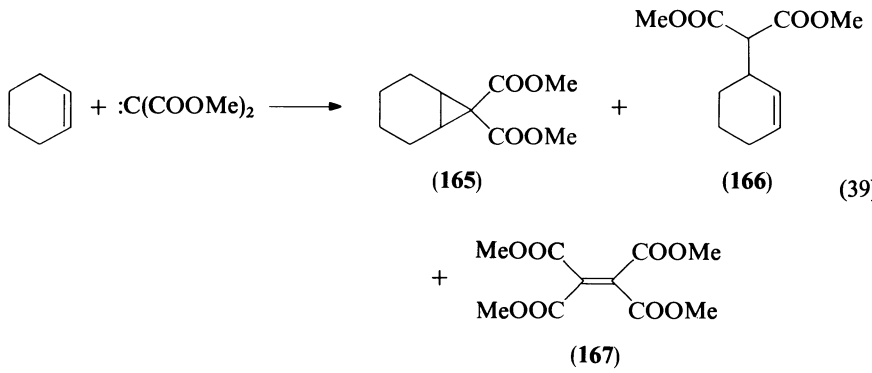
(38)

(161) (162, R = OCH_2Ph:62%) Ref. 96



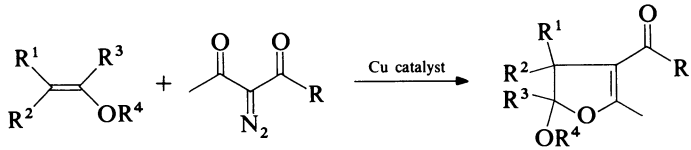
(163) (164, 40%) Ref. 97

When bis-methoxycarbonylcarbenoids react with olefins, three basic processes are observed. These are cyclopropanation, C–H insertion and carbene dimer formation



(39)

(tetrakis-methoxycarbonylethene) (equation 39)[99]. However, reaction of alkyl 2-diazo-3-oxobutanoates (**168**) or 3-diazo-2,4-pentanedione (**169**) with several vinyl ethers in the presence of bis(hexafluoroacetylacetonato)copper(II) gave dihydrofuran derivatives

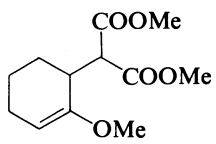


(40)

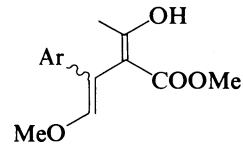
(168, R = OR')
(169, R = Me)

(170)

(170)[86]. Side-products of the latter reactions involved allylic C–H insertion products such as **171** and **172**[82,86].

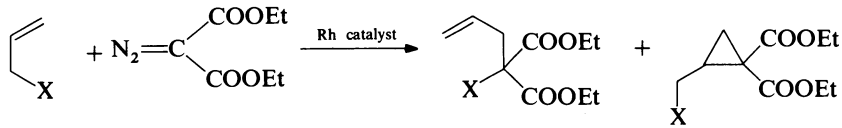


(171)



(172)

Diethyl diazomalonate (**142**) reacts with allyl bromide in the presence of a Rh catalyst to produce only minor amounts of the cyclopropane **174** together with the ylide derived malonate ester (**173**)[83]. With allyl chloride the electrophilic cyclopropane derivative **174** is produced predominantly (equation 41).



(142) (173) (174) (41)

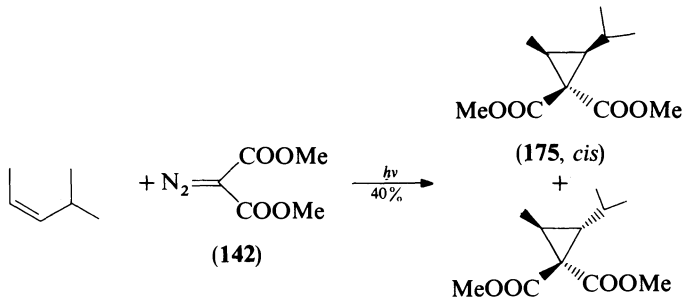
X = Cl, Br

Compared with results obtained for ethyl diazoacetate, reactions of diazomethane with allyl bromide produce a dramatic reversal in the relative reactivities of the carbenoid species towards the nucleophilic bromide and the carbon–carbon double bond. These results are in accord with a greater electrophilic selectivity of the dialkoxycarbonyl carbenoid intermediate relative to the ethoxycarbonyl carbenoid. That increasing the electrophilicity of the carbenoid intermediate can reverse its reactivity towards the nucleophilic heteroatom relative to the olefin is consistent with the nature of this

TABLE 1. Stereochemistry of the products in photochemical carbene addition to 4-methyl-2-pentene

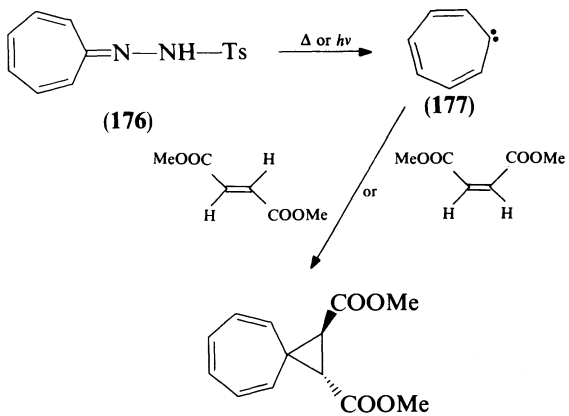
Alkene	Conditions	% **175** *cis*	% **175** *trans*
(*Z*)-4-Methyl-2-pentene	direct *hv*	92	8
(*E*)-4-Methyl-2-pentene	direct *hv*	10	90
(*Z*)-4-Methyl-2-pentene	$hv/Ph_2C{=}O$	10	90
(*E*)-4-Methyl-2-pentene	$hv/Ph_2C{=}O$	14	86

nucleophilic reaction [83]. Direct and sensitized irradiation of methyl diazomalonate affords singlet and triplet biscarbomethoxycarbene. Electrophilic cyclopropanes are formed on reaction with alkenes with substantial retention of stereochemistry from the singlet but with complete loss of stereochemistry from the triplet-generated species (equation 42 and Table 1)[100].



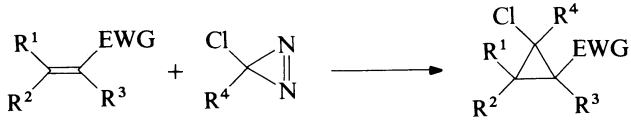
(142) (175, *cis*) (175, *trans*) (42)

Alkenes substituted with electron-withdrawing groups are capable of undergoing cyclopropanation with carbenes which do not carry an electron-withdrawing function, thus providing another means of generation of electrophilic cyclopropanes. The addition of cycloheptatrienylidene carbene (**177**) generated by thermolysis or photolysis of tropone tosylhydrazone (**176**), onto dimethyl maleate or dimethyl fumarate gave only the spiro compound **178** (equation 43)[101,102].



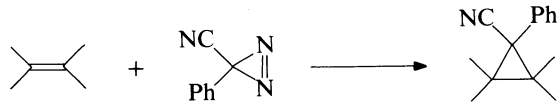
(176) (177) (178, 47%) (43)

Diazirines **179** and **181**, the cyclic structural isomers of diazo compounds, are often employed as entry to carbenes. By thermolysis of diazirines methoxychloro-[103], cyanophenyl-[104] and chlorophenyl carbenes[105] are generated and are able to undergo addition across olefinic derivatives (equation 44).



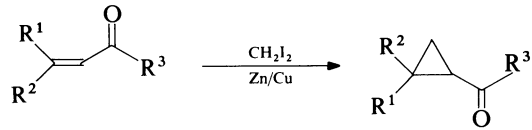
(179) (180, 48–97%)

R^4 = OMe, Ph (44)

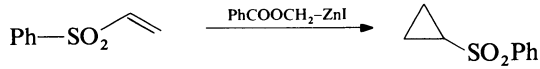


(181) (182)

The Simmons–Smith reaction is another alternative for the generation of electrophilic cyclopropanes, as exemplified for enones (equation 45)[106,107]. An analogous reaction using (benzoyloxymethyl) zinc iodide is able to convert phenyl vinyl sulphone (**184**) into cyclopropylphenyl sulphone (**185**)[108].

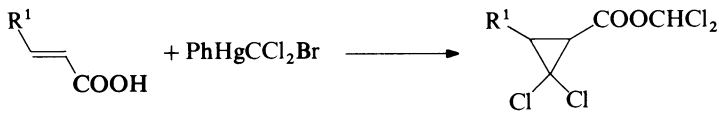


(183, 40–50%) (45)

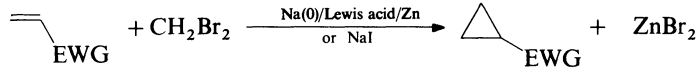


(184) (185, 18%)

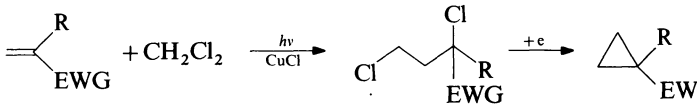
Cyclopropanation of alkenes carrying electron-withdrawing groups with dihalocarbenes does not take place under the normal reaction conditions unless the dihalocarbene is generated from trihalomethylphenylmercury compounds. By this procedure acrylonitrile was converted into 1-cyano-2, 2-dichlorocyclopropane in 78% yield[109] and other acrylic derivatives are transformed into dichloromethyl cyclopropane carboxylates (**186**) (equation 46). Treatment of electron-deficient olefins with dibromomethane in the presence of Ni(0) complex/Zinc/Lewis acid seems to be very effective for cyclopropanation[399].



(186)

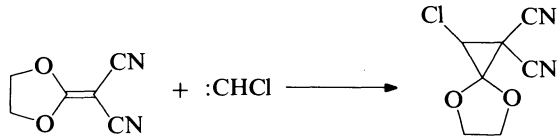


(46)



Adducts of dichloromethane and electron-deficient olefins are obtained using a CuCl-catalysed photochemical procedure. Electrochemical reduction further affords cyclopropane derivatives (equation 46)[111].

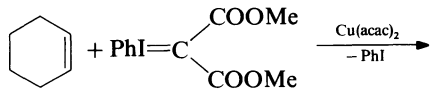
Reaction of chlorocarbene, generated from dichloromethyllithium, with the malononitrile derivative **187** affords minor amounts (2%) of the corresponding electrophilic cyclopropane (**188**) (equation 47)[112]. Reaction of phenyliodonium bis(methoxycarbonyl)



(47)

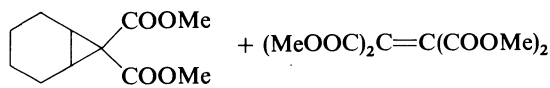
(**187**) (**188**)

methylide (**189**) with cyclohexene in the presence of bis(acetylacetonato) copper(II) gives rise to the formation of a mixture of the norcarane derivative (**165**) and the coupling product (**190**) (equation 48)[113]. This reaction proceeds via the intermediate formation of a carbene or carbenoid species.



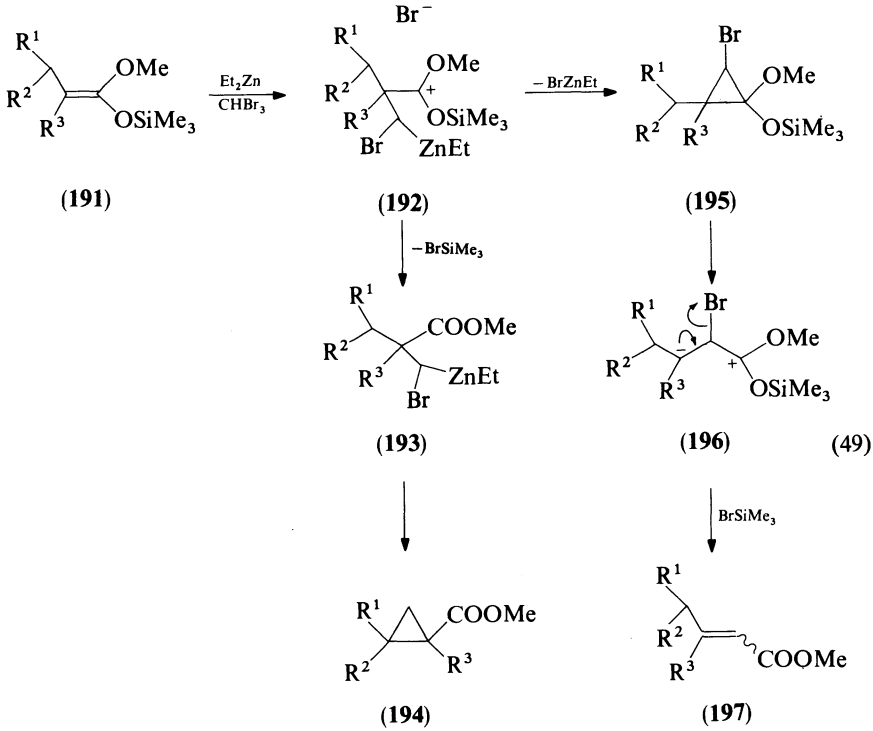
(**189**)

(48)



(**165**, 38%) (**190**, 41%)

An unprecedented cyclopropanation reaction was observed during the reaction of ketene alkylsilyl acetals (**191**) with bromoform-diethylzinc. When monosubstituted acetals were used, cyclopropanecarboxylic esters (**195**) were formed by a novel C–H insertion. When disubstituted ketene acetals were used, byproducts such as α,β-ethylenic esters (**197**) were also formed presumably via **196** (equation 49). This reaction provides a convenient method for the preparation of the bicyclo[3.1.0]hexane system and can be advantageously compared to the copper-catalysed intramolecular cyclization of unsaturated α-diazoketones[110].



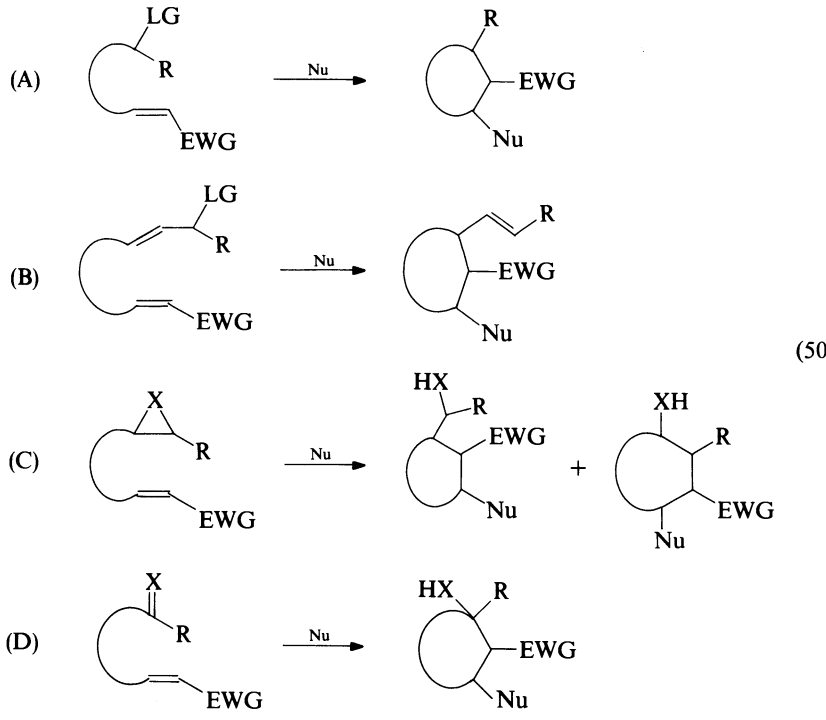
2. *Cyclopropanation via addition-nucleophilic substitution*

a. General remarks

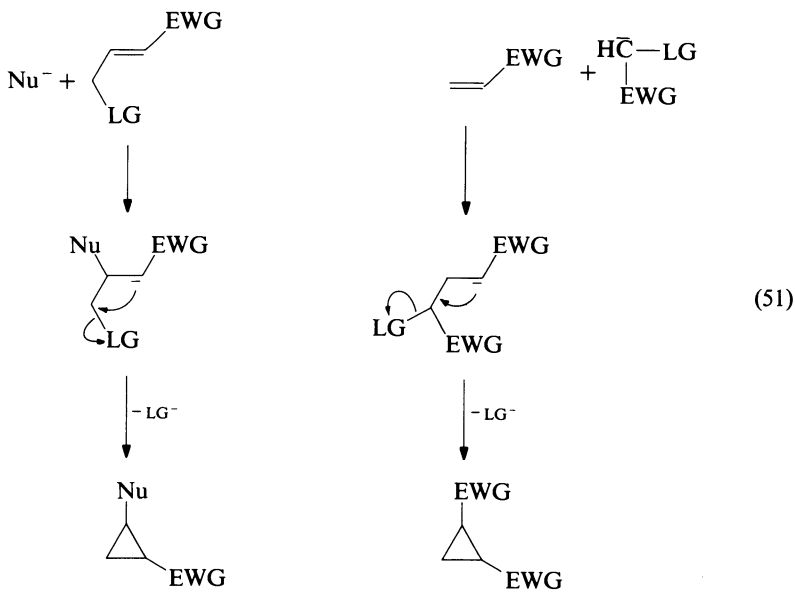
A large number of electrophilic cyclopropanes have been prepared via a route involving an addition of a nucleophilic species across an electron-deficient alkene followed by expulsion of a leaving group via an intramolecular substitution.

There are several alternatives for this type of reaction. The addition and substitution can be carried out in one step or the addition product can be isolated and treated with a base in a second step. In addition the leaving group can be a part of the alkene or can be attached to the attacking nucleophile.

Therefore a general term MIRC (*M*ichael *I*nitiated *R*ing-Closure) reaction was defined. This is applicable to a general set of transformations which are initiated by a conjugate addition to an electrophilic alkene to produce an enolate which subsequently undergoes an intramolecular ring-closure[400]. Four possible variations of MIRC reactions are illustrated in equation 50 where EWG = electron-withdrawing group, LG = leaving group and Nu = nucleophile. Route (A) especially has been widely used in the construction of electrophilic cyclopropanes. Many of the examples are limited to cases wherein a carbon, rather than a heteroatom-centred nucleophile initiates the process, and often to cases wherein the attacking centre is stabilized by a heteroatom which later serves as the leaving group in the ring-closure step. However, during the last ten years a limited number of electrophilic cyclopropanes have been prepared in which the leaving group is situated in the alkene moiety, as shown in equation 51.


(A)
LG
R
EWG
Nu
R
EWG
Nu
(B)
LG
R
EWG
Nu
R
EWG
Nu
(C)
X
R
EWG
Nu
HX
R
EWG
Nu
+
XH
R
EWG
Nu
(D)
X
R
EWG
Nu
HX
R
EWG
Nu

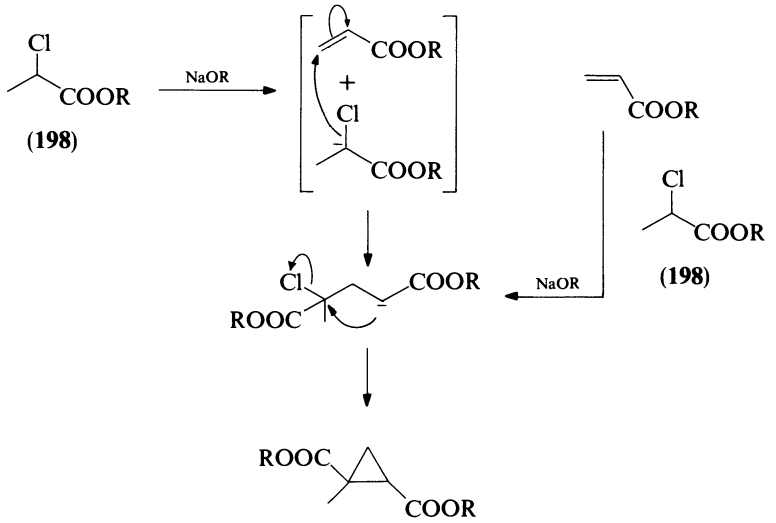
(50)


Nu⁻ +
EWG
LG
Nu
EWG
LG
- LG⁻
Nu
EWG
EWG
+
HC̄—LG
EWG
EWG
LG
EWG
- LG⁻
EWG
EWG

(51)

b. MIRC reactions with the leaving group in the attacking nucleophile

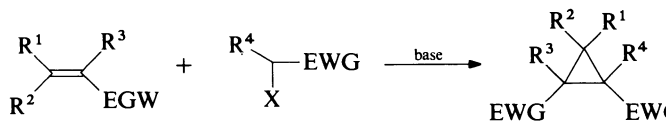
i. MIRC reactions with a halogen atom as leaving group. The general reaction, a Michael addition followed by an intramolecular S_N2 displacement, has been known for 35 years as a result of a reinvestigation of the reaction of ethyl 2-chloropropanoate with sodium methoxide. The original reported reaction product, diethyl 1,3-cyclobutanedicarboxylate, turned out to be diethyl 1-methyl-1,2-cyclopropanedicarboxylate (**199**, R = Et). The proposed reaction mechanism was supported by the formation of a similar product in the reaction of acrylic esters with α-chloropropionic esters (equation 52)[401]. McCoy established a general synthetic procedure for this base induced condensation of an α-halo ester with an α,β-unsaturated ester producing electrophilic cyclopropanes (McCoy reaction)[114–116,402].



(52)

(**199**, 35–70%)

Many electrophilic alkenes and stabilized α-halo carbanions (derived from α-halogenated ketones, esters, nitriles or sulphones) are reported to be applicable in this condensation (equation 53). Usually the reaction was carried out in the presence of sodium



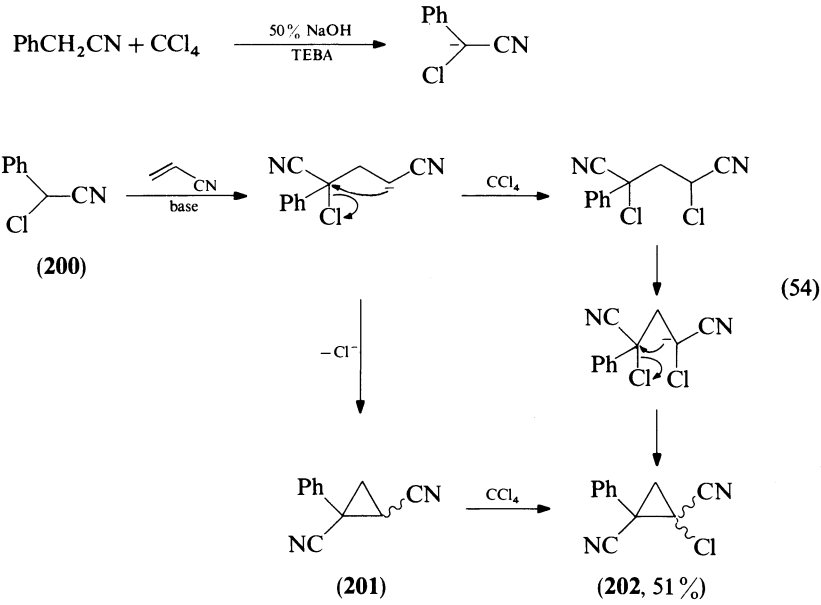
(53)

(40–90%)

EWG: COOR, COR, CN, SO_2R X = halogen

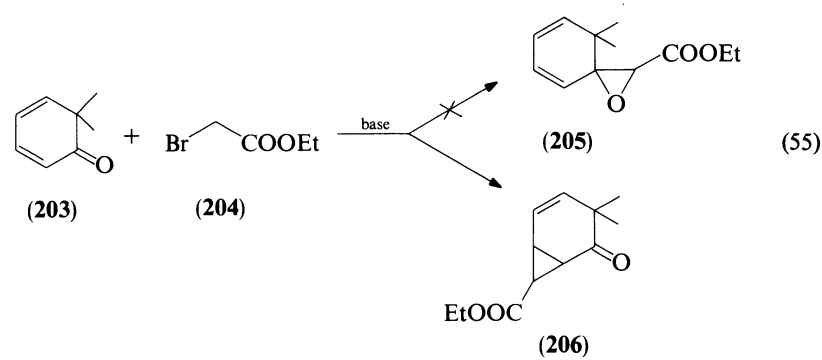
hydride, sodium alkoxides, potassium *t*-butoxide[117,118] or under phase-transfer-catalysed conditions, e.g. with 50% aqueous sodium hydroxide (TEBA)[119,120]. In a catalytic two-phase system, electrophilic cyclopropanes (**201**, **202**) are prepared by

reaction of acrylonitrile with α-chlorophenylacetonitrile (**200**) in the presence of carbon tetrachloride (equation 54)[120].



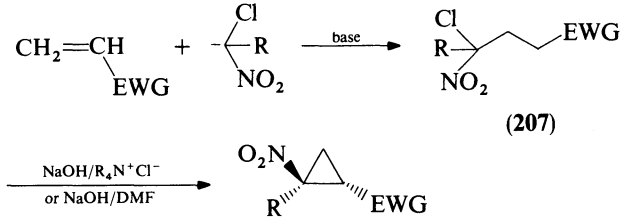
(54)

Treatment of α, β-unsaturated ketones with α-halo esters often results in oxirane (**205**) formation (Darzens reaction). However, the reaction of the dienone **203** with ethyl bromoacetate (**204**) produces the bicyclo[4.1.0]heptenone derivative **206** (equation 55)[121].



(55)

Examples are known in which first the Michael adducts (**207**) are formed and isolated followed by cyclization in a separate step in the presence of base (equation 56)[403]. The stereochemistry-determining step is the cyclization of the intermediate carbanion as illustrated below. There are two favoured conformations, I and II, of the carbanion–cation



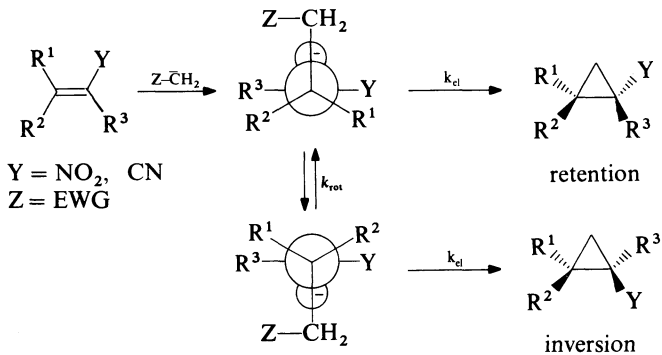
(56)

EWG: COOR, COMe, CHO, CN

(M^+) pair which lead to *Z* and *E* isomers respectively. The *E*/*Z* ratio depends on the nature of the solvent, the degree of association between the anionic species and the cation and the steric interactions[122, 123]. The decrease of solvent polarity and donor number, or the formation of a cationic bridge with the metal cation such as Li in conformation I favours formation of the Z-isomer. Steric strain between two large ester groups is minimized in the conformation II which leads to the *E*-isomer.

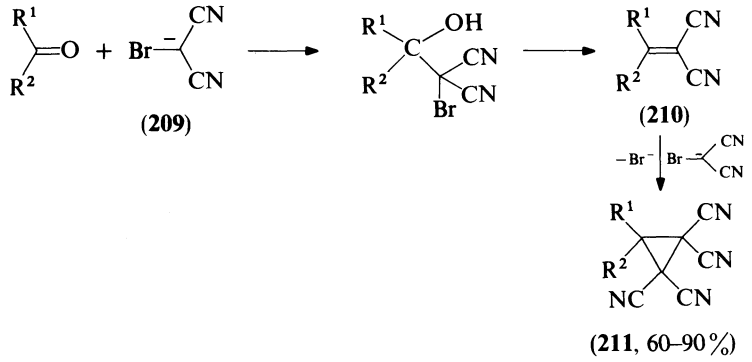
Stereochemical control can be achieved during the MIRC reaction of acrylonitrile with α-chloroacetonitrile producing 1,2-dicyanocyclopropanes. *Cis* compounds are favoured when a tetraalkylammonium salt is used in a two-phase system. This phenomenon is due to the fact that in the absence of the catalyst, the whole multistep process takes place at the phase boundary, whereas the catalytic reaction occurs inside the organic phase[124].

The stereoselectivity of cyclopropane ester formation could also be effected by using reagents supported on linear or cross-linked polymers. The most important effects were noted with chloromethylated polymers cross-linked with divinylbenzene[125]. The role of hyperconjugation in determining the stereochemistry of nucleophilic cyclopropanation of electrophilic alkenes has been studied and predicted[126]. In terms of equation 57 the



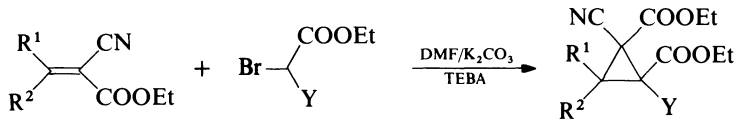
(57)

stereochemistry is determined in the cyclization step by competition between internal rotation around the C–C$^-$ bond and leaving group expulsion. If internal rotation (k_{rot}) is faster, loss of stereochemistry will be observed. If leaving group expulsion (k_{el}) is faster, retention will be observed. The barrier to rotation is largely influenced by hyperconjugation, but the calculated values for β-*Z*-CH_2-substituted carbanions are low. As a result, the outcome of the MIRC cyclopropanation is loss of stereochemistry in most cases[126]. The Widequist reaction which involves the reaction of ketones or aldehydes with bromomalononitrile (**209**) giving rise to 1,1,2,2-tetracyanocyclopropanes (**211**) can be regarded as a MIRC reaction of addition of the malononitrile carbanion across the *in situ* formed alkylidenemalononitrile (equation 58)[127,128]. It is clear that the MIRC reaction of alkylidenemalononitriles (**210**) with the bromomalononitrile carbanion (**209**) affords the same tetracyanocyclopropanes[128].

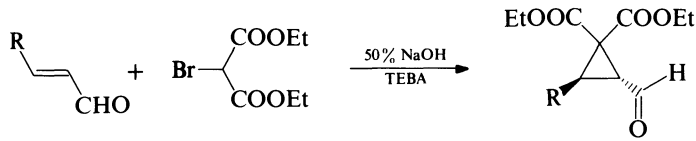


(209) (210) (211, 60–90%) (58)

A number of cyclopropanes with three and four EWGs (**47**, **214**) have been synthesized according to this procedure (equation 59)[129,130]. The formation of triethyl 1,2,3-tricyanocyclopropane-1,2,3-tricarboxylate (**216**) from ethyl bromocyanoacetate (**213**) with

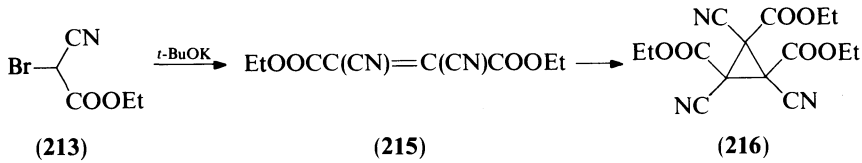


(**212**, Y = COOEt) (**213**, Y = CN) (**214**, Y = COOEt, CN, 35–81%) (59)



(**212**) (**47**, 43–48%)

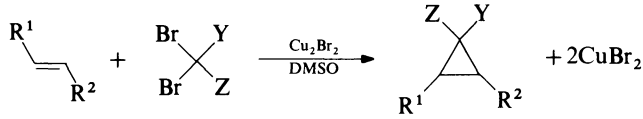
potassium *t*-butoxide can be also explained via a similar pathway involving an *in situ* generation of an electrophilic olefin (**215**) (equation 60)[131]. Until now both the attacking nucleophile and the alkene were substituted with electron-withdrawing groups. Few examples are known where either an activated nucleophile is attacking an unactivated



(213) (215) (216)

(60)

alkene or an unactivated nucleophile is added to an electrophilic alkene. Electrophilic cyclopropane derivatives are synthesized from aliphatic and acyclic alkenes and styrene derivatives by reaction with dibrominated activated methylene compounds (**217**) and Cu_2Br_2 in DMSO (equation 61). During the course of the reaction Cu_2Br_2 is converted into $CuBr_2$ which was isolated as a coordinated complex with two molecules of DMSO[132].



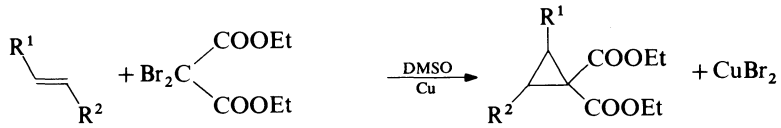
(61)

(217) (218)

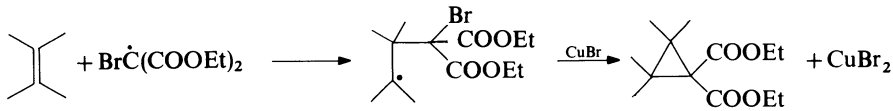
Y, Z = COOEt, CN

The reaction gives cyclopropanes in a non-stereospecific way. Approximately a 1:9 mixture of *cis* and *trans* isomers is obtained from both *cis*- and *trans*-β-methylstyrene.

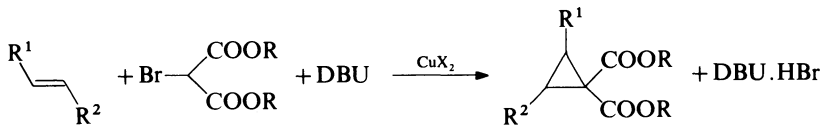
Similar cyclopropanation procedures involving 'copper' catalysis are encountered in the reaction of olefins with dibromomalonic esters (**217**) and Cu in dimethyl sulphoxide[133] and the reaction of olefins with monobromomalonic esters in the presence of DBU and catalytic amounts of copper(II) halide (equation 62)[134]. The reaction of ethyl dibromoacetoacetate (**219**) with styrene and copper produces the corresponding electrophilic



(**217**, Y = Z = COOEt) (**218**, Y = Z = COOEt: 10–80%)

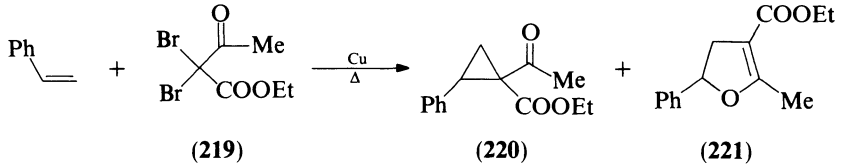


(62)

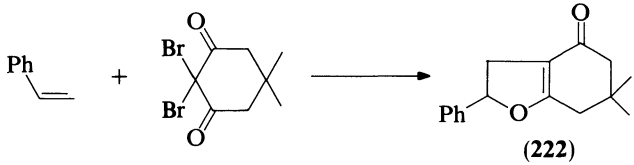


(**218**, Y = Z = COOR: 18–87%)

cyclopropane (**220**) together with minor amounts of a dihydrofuran derivative (**222**) (equation 63)[135].

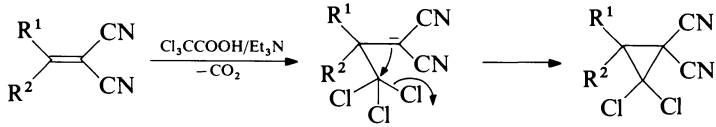


(**219**) (**220**) (**221**) (63)



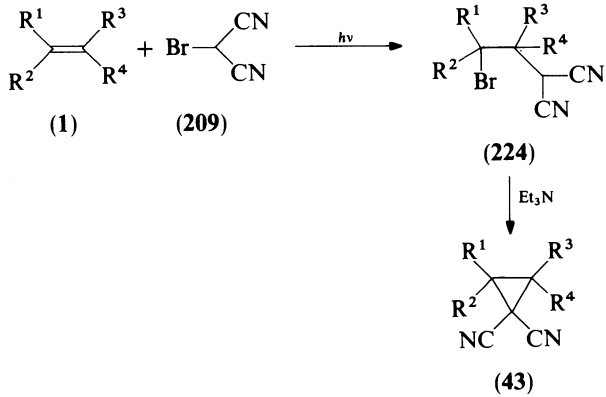
(**222**)

It was found that alkylidenemalononitriles **41** undergo 1,1-dichlorocyclopropane (**223**) formation by reaction with trichloroacetic acid. This reaction is presumed not to involve a dichlorocarbene addition, but instead a trichloromethylated carbanionic intermediate (equation 64)[136]. Substitution of one of the cyano groups by another EWG such as an ester or a sulphonyl function results in a very low yield of the corresponding cyclopropanes.



(**41**) (**223**, 44–78%) (64)

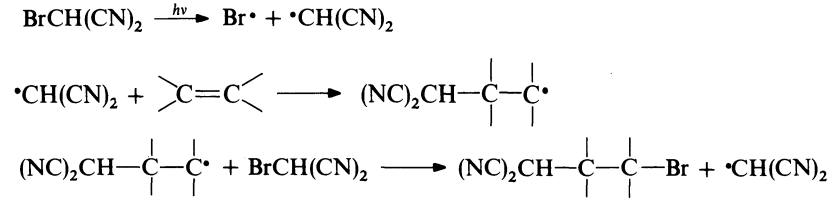
A highly efficient synthesis of geminally substituted dicyanocyclopropanes has been achieved by Boldt and coworkers using a free radical addition of bromodicyanomethane to aliphatic and cyclic alkenes under photolytic reaction conditions (equation 65)[137–140]. The intermediate addition products, i.e. 2-bromoalkylmalononitriles (**224**), are easily isolated and can be transformed into the dicyanocyclopropanes by treatment with



(**1**) (**209**) (**224**) (**43**) (65)

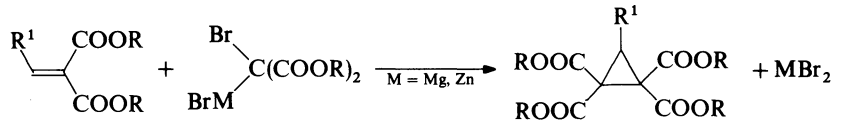
triethylamine. This reaction represents a typical example of a two-step MIRC in which the Michael addition product is isolated and undergoes a ring-closure with expulsion of the LG in a separate second step under the influence of a second reagent.

The free radical chain mechanism of the addition reaction of bromodicyanomethane to alkenes has been corroborated by inhibition experiments with oxygen and *t*-butylcatechol. The mechanism of equation 66 has been postulated. The ring-closure of the 2-bromoalkylmalononitriles gives rise to mixtures of *cis*- and *trans*-cyclopropanes.



(66)

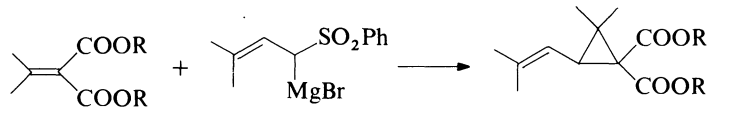
ii. MIRC reactions with a leaving group other than halogen. In addition to halogens a variety of leaving groups have been used in MIRC cyclopropanation of electron-deficient alkenes. Reaction of alkylidenemalonates with magnesium or zinc derivatives of diethyl dibromomalonate gives rise to alkylcyclopropane-1,1,2,2-tetracarboxylates (**225**) (equation 67). This procedure can be used for the conversion of α,β-unsaturated esters and ketones into the corresponding electrophilic cyclopropanes[141].



(67)

(**46**) (**225**, 69–76%)

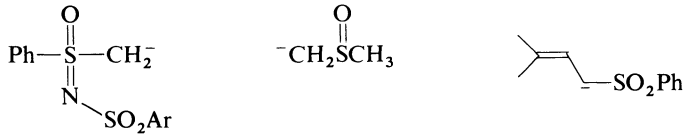
A similar procedure has been used in the synthesis of chrysanthemic acid derivatives (**228**) starting from isopropylidenemalonate (**226**) and a Grignard reagent (**227**) containing a sulphonyl function (equation 68)[142]. S-Containing leaving groups have also



(68)

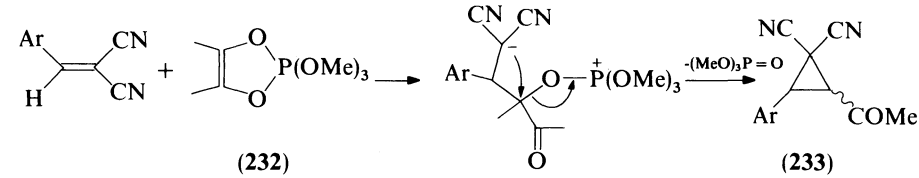
(**226**) (**227**) (**228**, 65%)

been utilized in cyclopropanation of olefins, e.g. the sulphoximine **229**[143], the dimsylate[144] anion (**230**) and the allylic sulphonylcarbanion (**231**)[145].

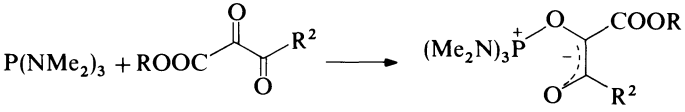


(**229**) (**230**) (**231**)

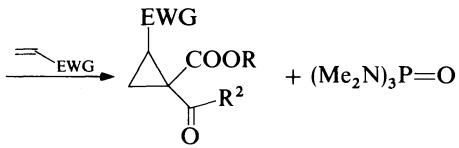
Reaction of benzylidenemalononitriles with 2,2,2-trimethoxy-1,3,2-dioxaphospholes (**232**) affords 2-acyl-1,1-dicyanocyclopropanes (**233**) via expulsion of trimethyl phosphate from the initially formed betaines (equation 69)[146]. In an analogous way, cyclopropanes



(**232**) (**233**)



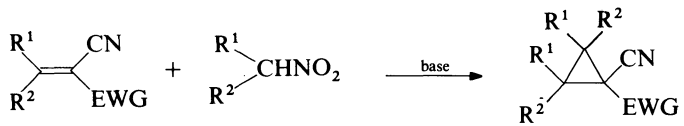
(**234**) (69)



(**235**)

R^2 = OR, Ph

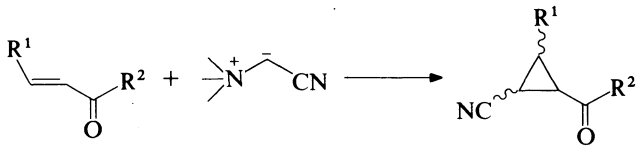
(**235**) have been prepared from betaines (**234**) by expulsion of hexamethylphosphortriamide[147]. Nitro functions have also been used as leaving groups. Addition of the anion derived from nitroalkanes across electron-deficient alkenes followed by intramolecular nucleophilic substitution affords electrophilic cyclopropanes in high yields. The reaction



(**236**) (70)

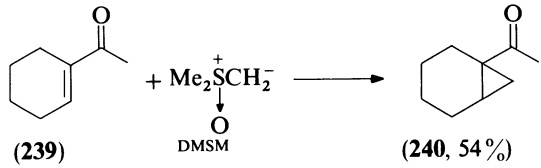
EWG = COOR, CN

gives good results only when at least one of the EWGs is a cyano function (equation 70)[148–150,397]. Expulsion of amines is observed during the cyclopropanation of monoactivated alkenes with cyanotrimethylammonium methylide (**237**) (equation 71)[151].



(**237**) (**238**) (71)

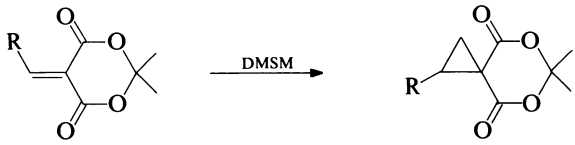
iii. MIRC reactions with ylides. Numerous cyclopropane derivatives have been synthesized via methylene transfer generated from sulphur ylides, such as dimethylsulphoxonium methylide, to electron-deficient alkenes. This is shown in the examples in



(239) DMSM (240, 54%) Ref. 152

(241) (107, 31%) Ref. 153

(38) (40, 50–70%) Ref. 154 (72)

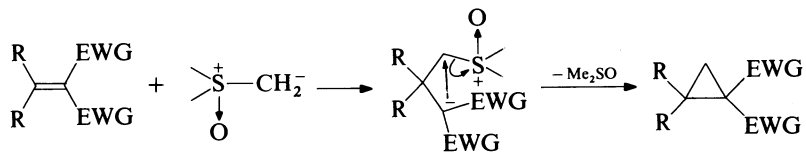


(44) (45, 40–85%) Ref. 155

(242) (243, 41–91%) Ref. 156

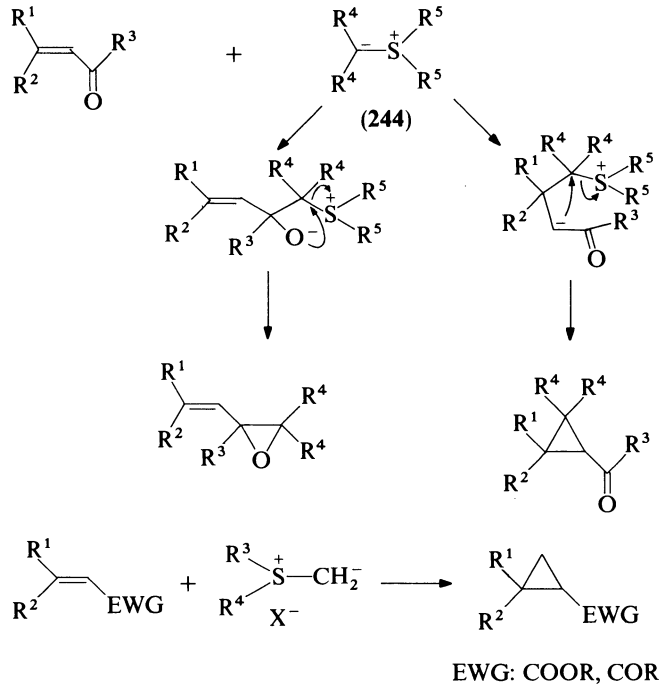
EWG: COOR, CN, SO_2Me

equation 72[152–156]. This cyclopropanation involves the formation of zwitterionic intermediates (equation 73).



(73)

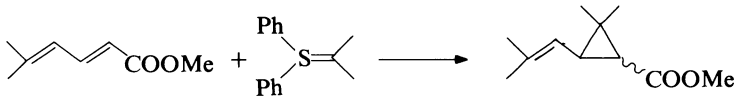
Although sulphonium salts (**244**) are known to react with α,β-unsaturated ketones with formation of the corresponding oxiranes[152,157], several α,β-unsaturated ketones[158], esters[158–160] and lactones[161] have been converted into cyclopropanes by treatment with these reagents (**244**) (equation 74). Also diphenyl- and benzylidenesulphuranes (**245**, **246**)



(74)

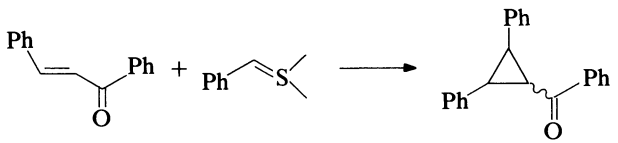
EWG: COOR, COR

have been used in cyclopropanations of olefins substituted with electron-withdrawing groups (equation 75). Cyclopropyl steroids are formed when γ-oxoammonium salts (**250**)



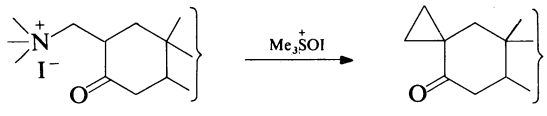
(**245**) (**247**, 73%) Ref. 160

(75)



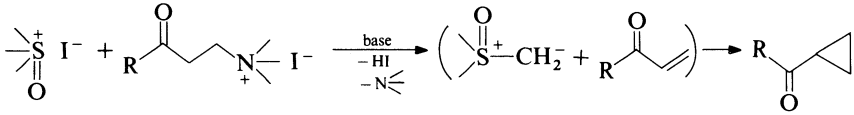
(**248**) (**246**) (**249**, 74%) Ref. 157

are treated with trimethylsulphoxonium iodide (equation 76)[162]. This reaction proceeds via an *in situ* formation in alkaline medium of dimethyloxosulphonium methylide and a



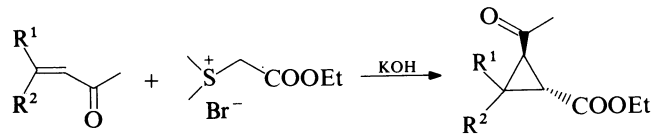
(250) (251)

(76)



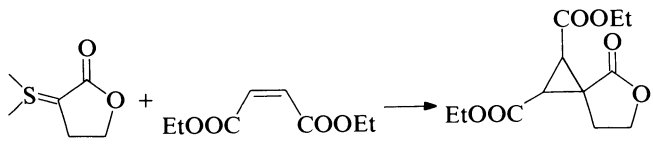
(252)

vinylketone generated from a Hofmann degradation of the quaternary Mannich base. Introduction of an EWG in a cyclopropane can also be performed via sulphur ylides bearing an EWG, such as dimethylsulphonium phenacylide[163] and sulphonium alkoxycarbonyl methylide (equation 77)[156, 164–166].



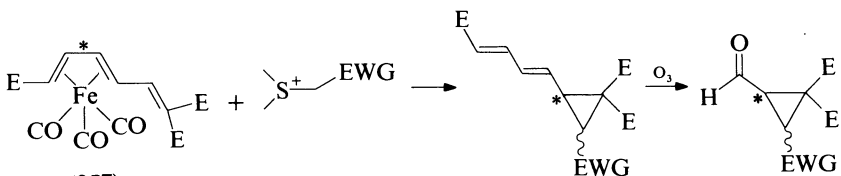
(253) (254) Refs 166, 167

(77)



(255) (256, 95%) Ref. 168

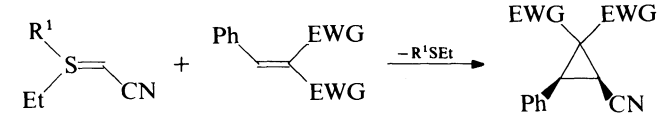
Chiral cyclopropanes geminally substituted with two EWGs (**259**) are obtained when alkenes, complexed with Fe carbonyls (**257**), are treated which sulphur ylides bearing an EWG (equation 78)[169]. Reaction of cyanosulphoniummethylide (**260**) with electron-



(257) (258) (259)

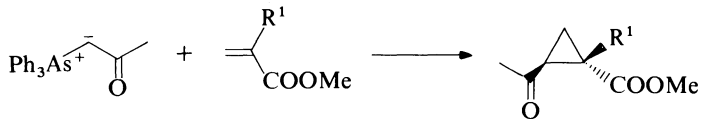
E = COOR (78)

deficient olefins (**261**) gives rise to the formation of electrophilic cyclopropanes (**262**) substituted with three electron-withdrawing groups (equation 79)[170]. While stabilized

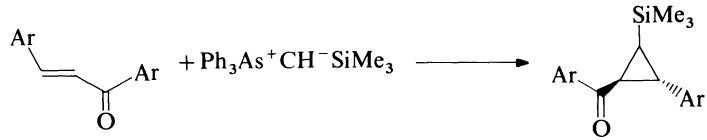


(260) (261) (262) (79)

phosphorus ylides did not form cyclopropanes on reaction with α,β-unsaturated carbonyl compounds, acetylmethylene triphenylarsorane (**263**) reacts with α,β-unsaturated esters with formation of *trans*-1,2-disubstituted cyclopropanes (**264**) (equation 80)[171].

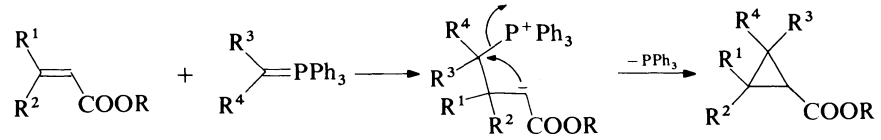


(263) (264, 65–95%) (80)

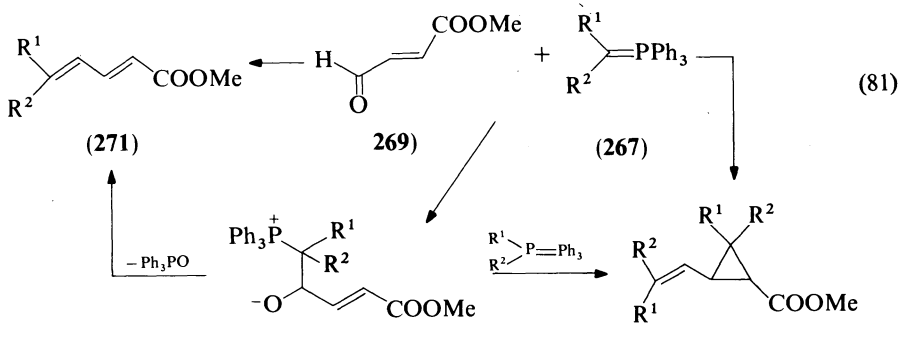


(265) (266, 30–50%)

Trimethylsilylmethylenetriphenylarsorane, in contrast to trimethylsilylmethylenesulphurane, could also react with substituted chalcones to give silylcyclopropanes (**266**) (equation 80)[172]. Reaction of phosphoranes (**267**) with crotonates gives rise to electrophilic cyclopropanes (**268**) (equation 81)[173–177]. However, the reaction of methyl



(267) (268, 55–70%)



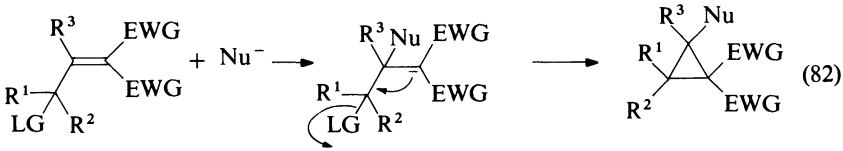
(271) 269) (267) (81)

(270) (272, R^1, R^2 = Me, $(CH_2)_4$)

3-formylpropenoate (**269**) with phosphoranes (**267**) seems to be dependent on the substitution pattern of the phosphorane. Only cyclopropanation occurs with isopropylidene and cyclopentylidene phosphorane. In other cases diene carboxylates (**271**) are formed[174,175]. A second equivalent of the phosphorane reacts only with the betaïne (**270**) under carefully controlled conditions to give **272** (equation 81).

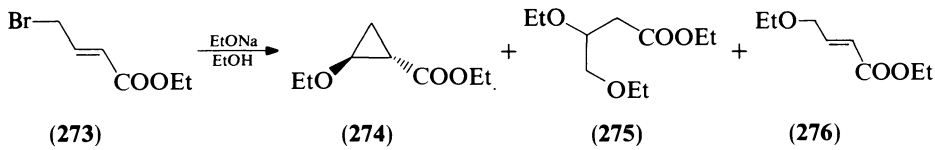
c. MIRC reactions with the leaving group in the electrophilic substrates

Reaction of nucleophilic species with alkenes substituted with a leaving group is an excellent procedure for the construction of electrophilic cyclopropanes substituted with a variety of other functional groups. In most cases the alkene is substituted with one or two electron-withdrawing groups although a number of alkenes without electron-withdrawing groups are known to undergo addition and ring-closure. The leaving group can occupy various positions in the electron-deficient alkenes, among others the α-position or the allylic position in relation to the EWG. Undoubtedly the best studied reaction consists of the MIRC reaction of electrophilic allylic halides with a variety of nucleophiles giving rise to cyclopropanes geminally substituted with two electron-withdrawing groups (equation 82)[178–192].

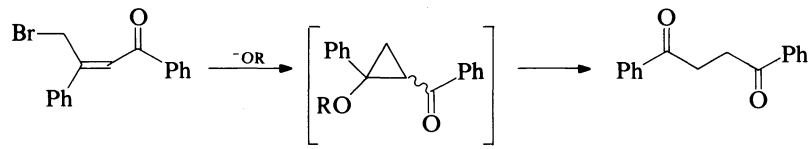


(82)

It is clear that during nucleophilic reactions of allylic halides carrying one EWG various other reaction pathways can occur in addition to MIRC reactions, e.g. addition, substitution, rearrangement and elimination[193–196]. For example, reaction of ethyl 4-bromocrotonate (**273**) with sodium ethoxide in ethanol only affords minor amounts of the 2-ethoxycyclopropane carboxylate (**274**) in addition to the substitution (**276**) and the addition–substitution (**275**) product (equation 83)[197]. Nevertheless, a cyclopropane



(**273**) (**274**) (**275**) (**276**)



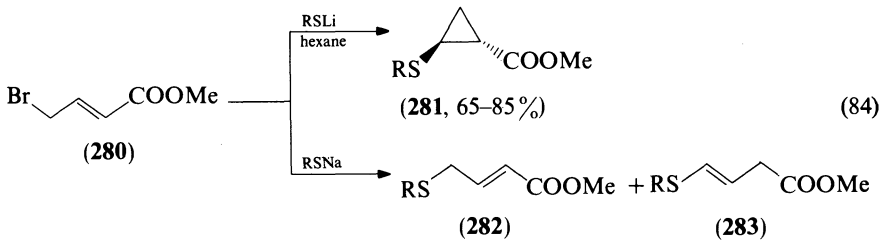
(**277**) (**278**) (**279**, 49%)

(83)

derivative, formed by a MIRC reaction, has been postulated as an intermediate during the reaction of 4-bromo-1,3-diphenyl-2-buten-1-one with alkoxides, but ring-opening afforded 1,4-diphenyl-1,4-butanedione (**279**) (equation 83)[198].

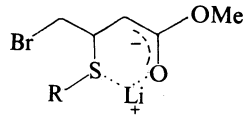
In most cases treatment of olefins, substituted with one EWG, with nucleophiles does not give rise to MIRC products, unless the reaction is carried out using particular

substrates or nucleophiles or under appropriate reaction conditions. While methyl 4-bromocrotonate (**280**) is known to undergo S_N2 displacement[199,200] reactions with mercaptides it was found that treatment of this methyl ester with lithium *s*-butyl- or *t*-butylmercaptide furnishes cyclopropane derivatives (**281**) (equation 84)[201].



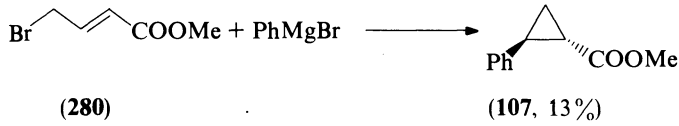
(84)

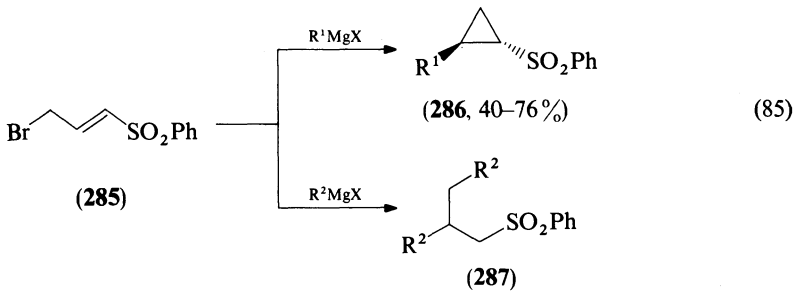
Consideration of the solvent and gegen ion effects suggests that solvation and coordination effects are important in determining the course of the reaction. When lithium is the gegen ion and in solvents such as CH_2Cl_2, THF, ether, benzene and pentane, the lithium metal is coordinated both with sulphur and with the carbonyl oxygen (cf. **284**), thereby



(**284**)

holding the attacking sulphur atom in close proximity to the β-carbon atom—the observed site of predominant attack. When the solvent is changed to DMF or HMPA, the solvent solvates the metal and effectively removes its effect upon the course of the reaction, resulting in γ-attack. The effect of gegen ion change can be accounted for by simply realizing that in progressing from Li^+ to Na^+ to K^+, the metals become progressively less effective in their ability to coordinate with oxygen, thereby allowing more access to the γ-carbon atom.





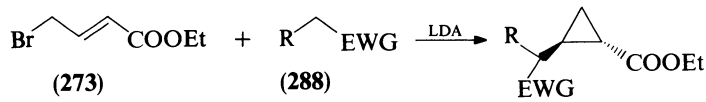
(85)

R^1 = $CH_2=CH-CH_2$, $HC\equiv CCH_2$, Ph, $PhCH_2$

R^2 = Me, Et, *t*-Bu

Inverse addition of phenylmagnesium bromide to methyl 4-bromocrotonate affords 13% of the cyclopropane product (equation 85). Alkyl magnesium bromides do not show any MIRC product at all[202]. On the other hand 3-bromo-1-(phenylsulphonyl)-1-propene (**285**) reacts with Grignard reagents derived from allyl bromide, propargyl bromide, bromobenzene and benzyl chloride to furnish 2-substituted cyclopropyl phenyl sulphones (**286**). Alkylmagnesium halides do not give cyclopropanation (equation 85)[203].

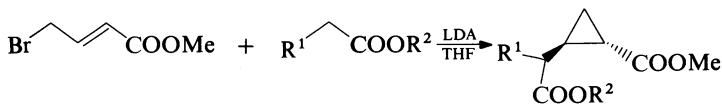
Ethyl 4-bromocrotonate (**273**) reacts as a Michael acceptor with carbanions derived from **288** stabilized by a sulphur substituent (sulphone, sulphoxide, sulphide). The conjugated addition is followed by displacement of bromide affording various cyclopropanecarboxylates (**289**) (equation 86)[204]. Also the reaction of methyl 4-bromocrotonate



(**273**) (**288**) (**289**, 61–77%)

EWG: SO_2Ph, SOPh, SPh

(86)

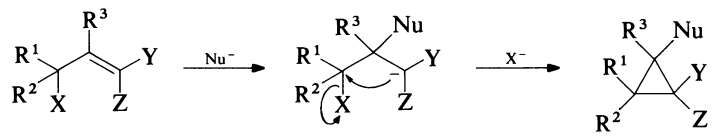


(**280**) (**290**, 37–73%)

R^1 = alkyl, $PhCH_2$, $PhCH_2CH_2$

(**280**) with lithium ester enolates gives rise to cyclopropanation when THF is used as a solvent (equation 86). Reaction in HMPA produces a mixture of the substitution and the MIRC products[205].

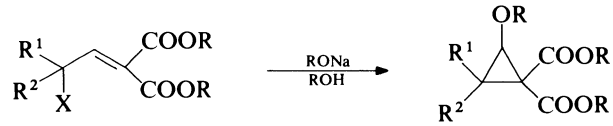
In contrast to the allyl halides with one EWG, nucleophilic attack on double bond activated allyl halides (**291**) normally gives rise to substituted electrophilic cyclopropanes (**293**) or compounds derived therefrom (equation 87). The formation of these cyclopropanes is strongly dependent on the reaction conditions, the nature of the nucleophiles, the



(**291**) (**292**) (**293**) (87)

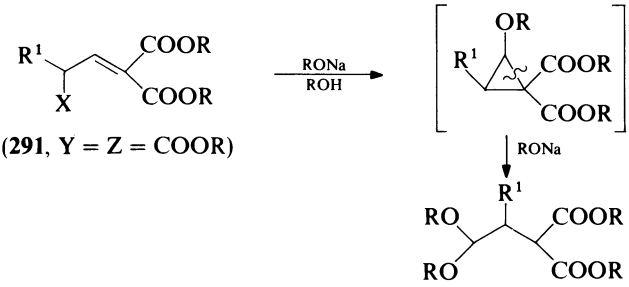
activating groups and the substitution pattern of the allyl halides. Reaction of the doubly activated allyl halides with equimolar amounts of sodium alkoxides in the corresponding alcohol affords only 2-alkoxy-substituted cyclopropanes (**294**) using tertiary allyl halides (**291**) (R^1 and $R^2 \neq H$) geminally substituted with two ester functions and $R^3 = H$.

Primary and secondary allyl halides (R^1 or $R^2 = H$), all the allyl halides with R^3 = alkyl, aryl and tertiary halides substituted with one or two cyano functions (Y and/or Z = CN) give rise to acetal (**295**, **296**, **297**) formation via ring-opening of the non-isolable cyclopropanes by further reaction with the alcohol (equation 88)[178,179,181,184,185,188,191,192,206]. However, reaction of 2-bromo-2-methyl-1-phenyl-



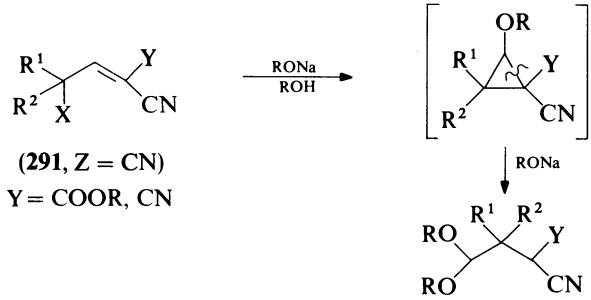
(**291**, Y = Z = COOR)
R^1, R^2 = alkyl

(**294**, 40–95%)



(**291**, Y = Z = COOR)

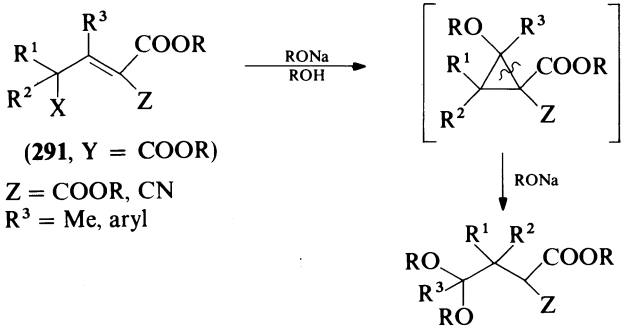
(**295**, 50–90%)



(**291**, Z = CN)
Y = COOR, CN

(**296**, 40–85%)

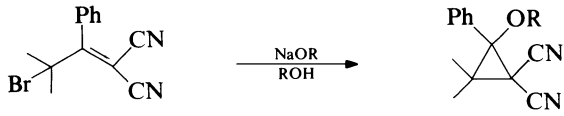
(88)



(**291**, Y = COOR)
Z = COOR, CN
R^3 = Me, aryl

(**297**, 40–90%)

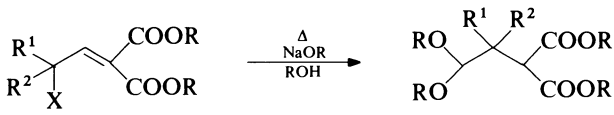
propylidenemalononitrile (**298**) with sodium alkoxides in the corresponding alcohols furnishes the corresponding 1,1-dicyanocyclopropanes (**299**) (equation 89)[188].



(89)

(**298**) (**299**, 68–89%)

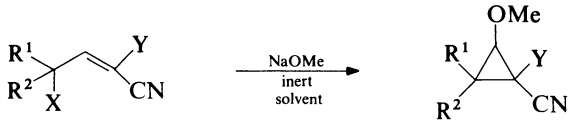
The tertiary allyl halides (**291**, Y=Z=COOR) furnish acetals (**295**) on heating with two equivalents of the alkoxide in the corresponding alcohol (equation 90)[181]. On the other



(90)

(**291**, Y = Z = COOR) (**295**, 70–90%)

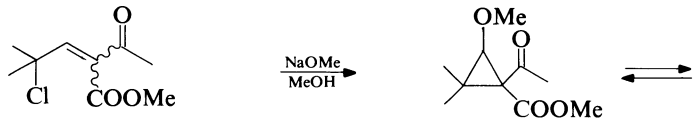
hand, treatment of tertiary allyl halides (R^1; $R^2 \neq H$; $R^3 = H$) with sodium methoxide in an inert solvent (acetonitrile, dioxan) affords the corresponding 2-methoxycyclopropanes (**294a**) without rearrangement (equation 91). However, the primary and secondary allyl



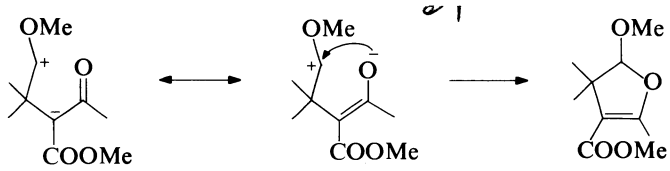
(91)

(**291**, Z = CN) (**294a**)

bromides and the allyl halides with R^3 = alkyl or phenyl do not show any reaction under the same reaction conditions. In particular cases, reaction of doubly activated allyl halides give rise to deviating results. Treatment of methyl 2-acetyl-4-chloro-4-methyl-2-pentenoate (**291**, Y=COOR, Z=COMe), with methanolic sodium methoxide under reflux produces a dihydrofuran derivative **301** via rearrangement of the intermediate cyclopropane **300** (which is isolable at 0 °C) (equation 92)[191].



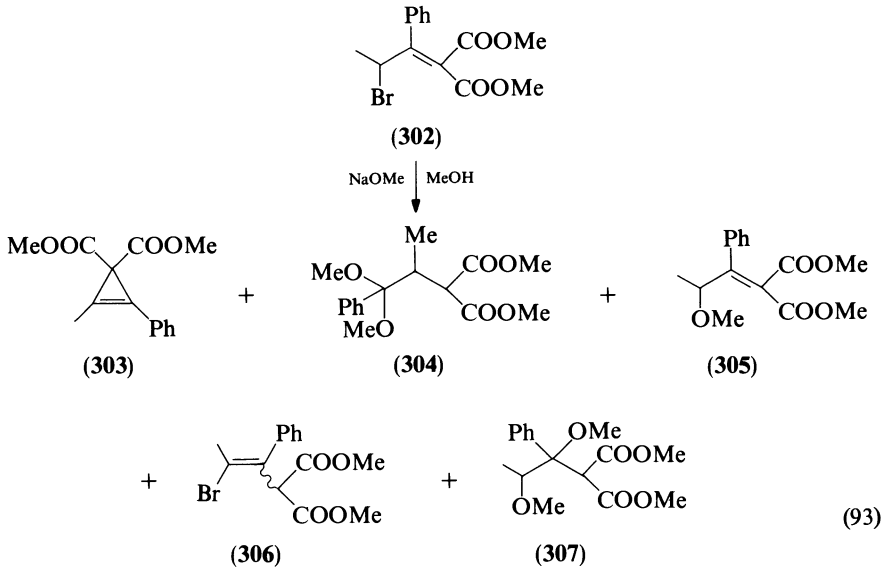
(**291**, Y = COOMe, Z = COMe) (**300**)



(92)

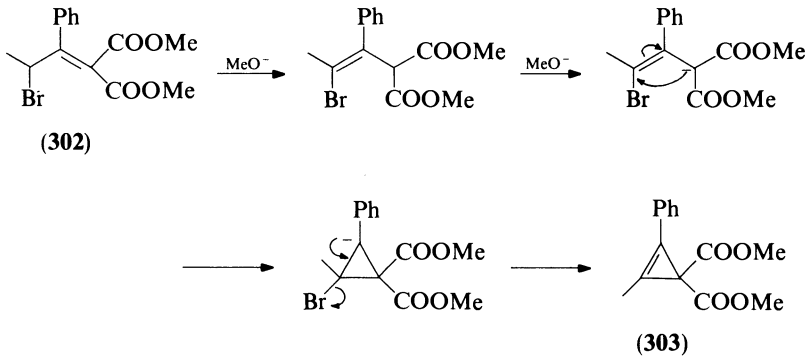
(**301**)

The reaction between dimethyl 2-bromo-1-phenylpropylidenemalonate and sodium methoxide in methanol affords a complex reaction mixture consisting of dimethyl 2-methyl-3-phenyl-2-cyclopropene-1,1-dicarboxylate (**303**, 19%), dimethyl (2,2-dimethoxy-1-methyl-2-phenylethyl)malonate (**304**, 4%), dimethyl 2-methoxy-1-phenylpropylidenemalonate (**305**, 11%), dimethyl 2-bromo-1-phenyl-1-propenylmalonate (**306**: *E*-isomer, 10%; *Z*-isomer, 13%) and dimethyl (1,2-dimethoxy-1-phenylpropyl)malonate



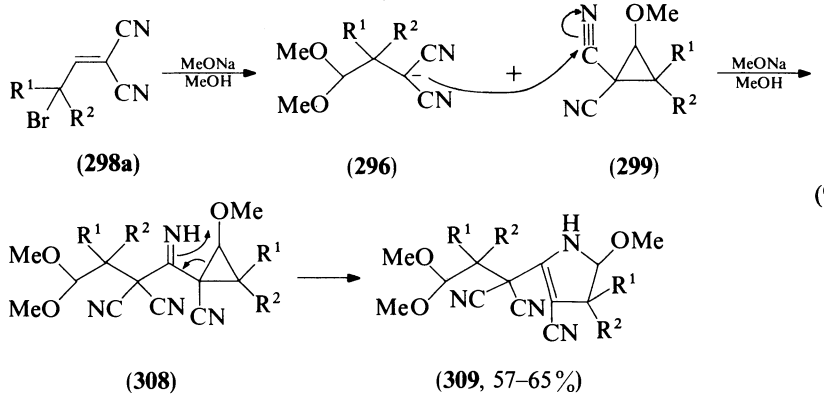
(93)

(**307**, 33%) (equation 93)[187]. The formation of the cyclopropene derivative (**303**) can possibly be explained via a mechanism as depicted in equation 94.



(94)

The reaction of brominated alkylidenemalononitriles (**298**) with sodium methoxide in methanol leads to Δ^2-pyrrolines (**309**) in a Thorpe-type reaction involving an addition of the anion **296** to the cyano function in the intermediate cyclopropane **299** (equation 95)[180]. The acetals (**308**) can be isolated if the malononitriles are treated with pyridine-methanol.

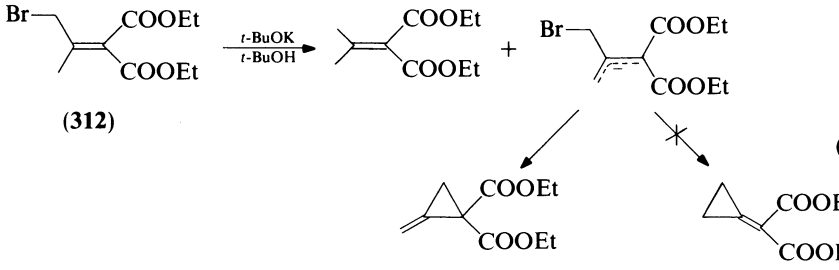


(298a) (296) (299)

(95)

(308) (309, 57–65%)

Diethyl 2-bromo-1-methylethylidenemalonate (**312**) reacts with *t*-BuOK in *t*-butanol giving rise to diethyl 2-methylidenecyclopropane 1,1-dicarboxylate (**310**) together with the debrominated product (equation 96)[207]. Treatment of 2-bromo-2-methyl-1-(*o*-bromomethylphenyl)propylidenemalononitrile (**312a**) with one equivalent of sodium

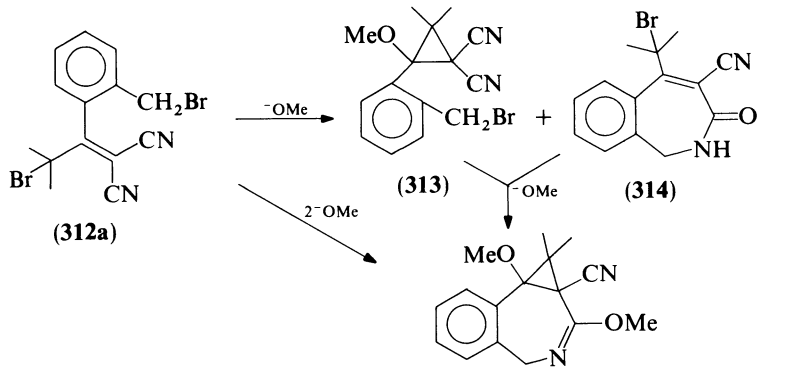


(312)

(96)

(310) (311)

methoxide furnishes a mixture of the cyclopropane **313** and a benzazepine derivative (**314**). When the allyl bromide is reacted with two equivalents of methoxide or when the cyclopropane (**313**) or benzazepine (**314**) react with one equivalent of methoxide ion the tricyclic cyclopropane **315** is formed as the sole product (equation 97)[189].

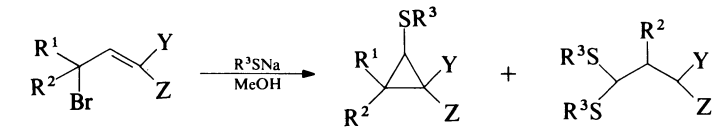


(312a) (313) (314)

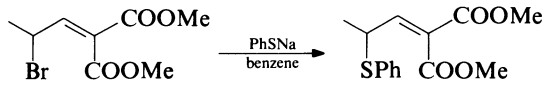
(97)

(315)

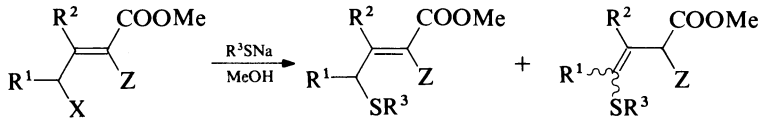
In contrast to the reaction of doubly activated allyl halides with alkoxides, treatment with sodium thiolates in methanol always gives rise to 2-alkylthio- and 2-arylthiocyclopropanes (**316**) in a very fast reaction. Only in a few cases and under rigorous reaction conditions dialkylthioacetals (**317**) are isolated (equation 98)[181,191]. Two exceptions have



(**291**, Y = COOR) (**316**) (**317**, R^1 = H)



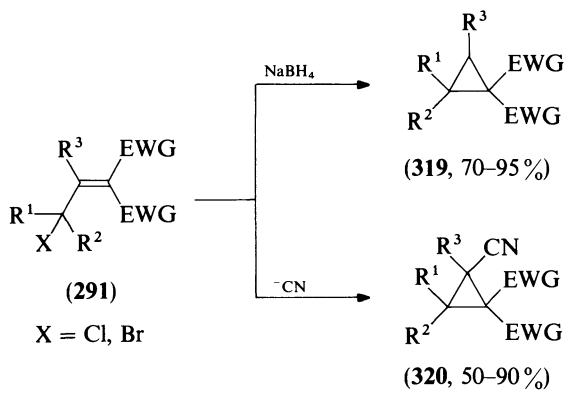
(**291**, Y, Z = COOMe) (**318**) (98)



(**291**, Y = COOMe)

been mentioned where reaction with mercaptides affords 'substitution' products (equation 98). However, it is not clear if these products are derived from an S_N2 reaction or from a rearrangement of intermediate cyclopropanes[184,206].

The most general formation of electrophilic cyclopropanes involving nucleophilic attack on electrophilic allyl halides occurs when sodium borohydride and sodium or potassium cyanide is used as a nucleophilic species (equation 99)[178,179,181,183,184,186–188,190–192,206]. No ring-opening is observed even under



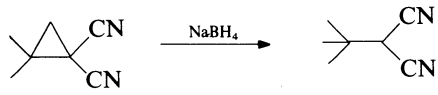
(**291**)

X = Cl, Br

(**319**, 70–95%)

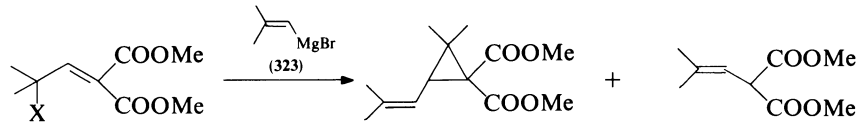
(**320**, 50–90%) (99)

drastic reaction conditions, except for the ring-opening of 1,1-dicyano-2,2-dimethylcyclopropane (**321**) giving rise to *t*-butylmalononitrile (**322**) (equation 100)[183].

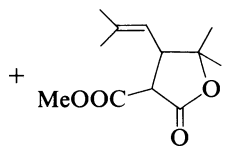


(**321**) (**322**) (100)

Dimethyl 3-(2-methyl-1-propenyl)-2,2-dimethylcyclopropane-1,1-dicarboxylate (**324**) is synthesized by the reaction of (2-halo-2-methylpropylidene)malonate (**291**) with 2-methyl-1-propenylmagnesium bromide (**323**). The cyclopropane is accompanied by the malonoester (**325**) and a butanolide (**326**) formed by nucleophilic attack of an ester enolate (equation 101)[182].

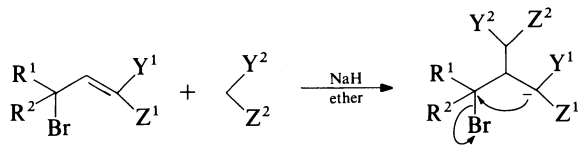


(**291**, Y = Z = COOMe) (**324**) (**325**) (101)

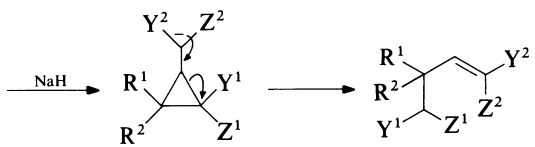


(**326**)

The reaction of electrophilic allyl halides with active methylene functions give a completely different course although intermediate electrophilic cyclopropanes (**327**) play a crucial role. Ring-opening of the cyclopropanes affords compounds **328** in which the electron-withdrawing groups are rearranged to the allylic position (equation 102)[208]. This



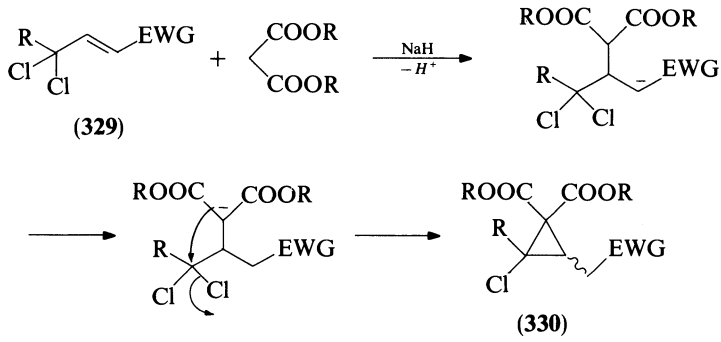
(**291**)



(**327**) (**328**) (102)

Y^1; Z^1; Y^2; Z^2: COOR, CN, COR

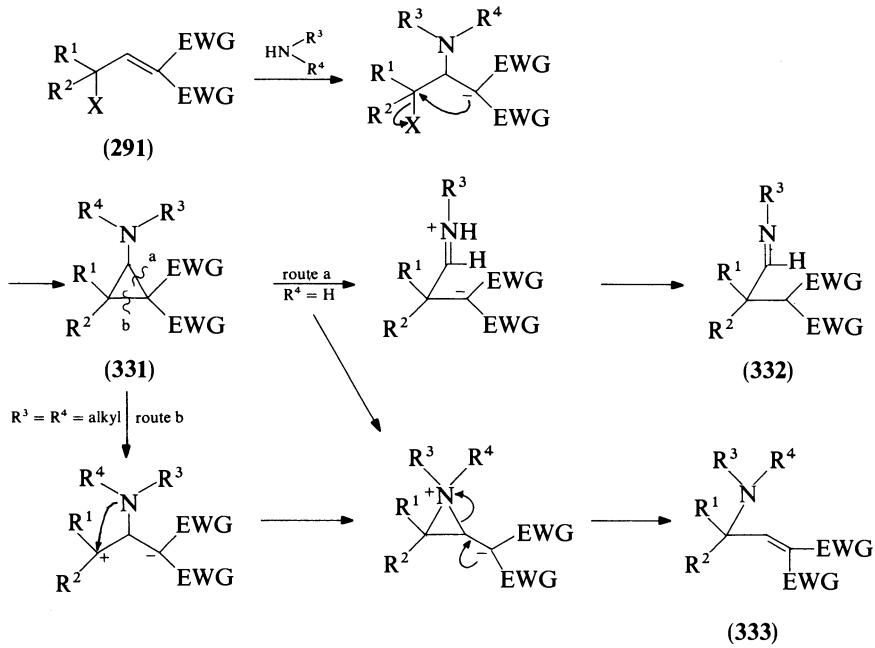
reaction pathway is confirmed by the reaction of monosubstituted allylic dihalides (**329**) with active methylene functions affording chlorinated electrophilic cyclopropanes (**330**) (equation 103)[208].

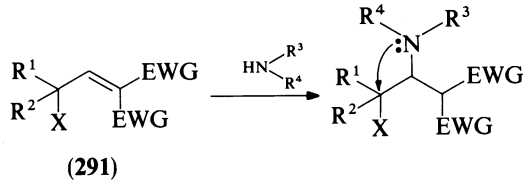


(103)

During the reaction of the doubly activated allyl halides with primary and secondary amines no 2-amino-substituted cyclopropane derivatives could be isolated, but instead ring-opened products are formed. Primary amines give rise to the formation of aldimines (**332**) while secondary amines afford formally 'substitution' products (**333**)[184,206]. The formation of these products can be explained by ring cleavage of non-isolable electrophilic 2-aminocyclopropanes (**331**) as outlined in equation 104.

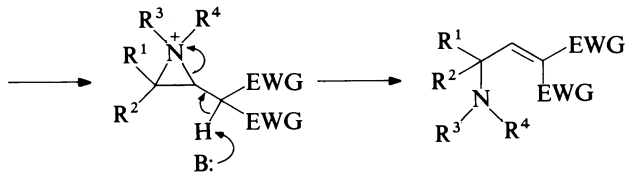
An alternative mechanism for the formation of the substitution products **333** entails the intermediacy of an aziridinium ion (**334**). Curiously, reaction of these allyl halides (**291**,





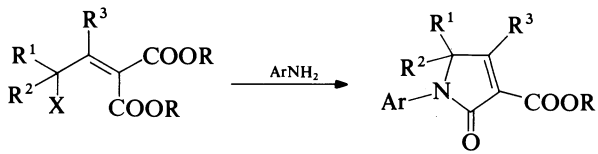
(291)

(104)



(334) (333)

Y=Z=COOR) with primary arylamines furnishes 'substitution' products which undergo ring-closure with formation of pyrrolinones (335) (equation 105)[206]. The intermediacy of

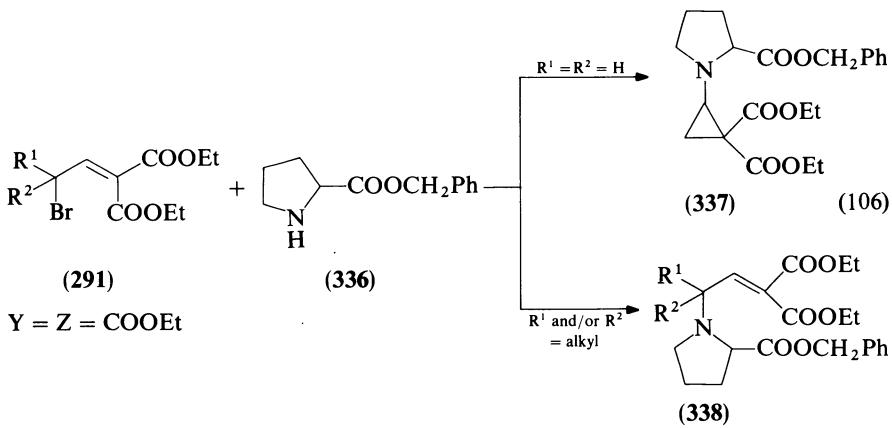


(291) (335)

Y = Z = COOR

(105)

2-aminocyclopropanes (331) is proven by the fact that reaction of proline benzyl ester (336) with a diethyl 2-bromoethylidenemalonate (291) affords the corresponding cyclopropane (337). Secondary or tertiary allyl bromides, however, give the 'substitution' products 338 (equation 106)[209].

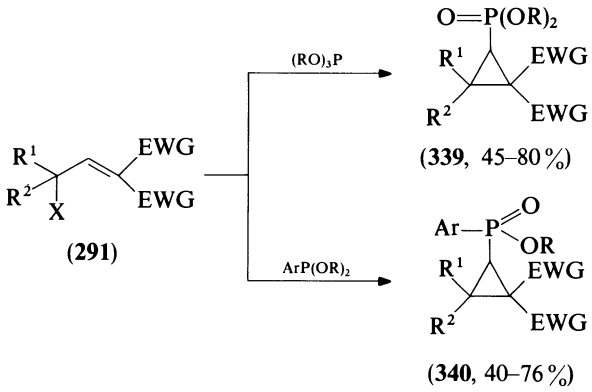


(291) (336) (337) (338)

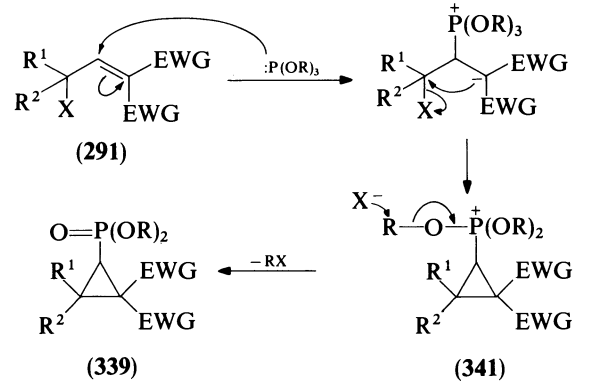
Y = Z = COOEt

(106)

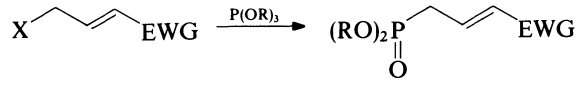
Finally, attack of phosphorus nucleophiles such as trialkyl phosphites and dialkyl phenylphosphonites onto doubly activated allyl halides yields 2-phosphono- (**339**) and 2-phosphino-substituted electrophilic cyclopropanes (**340**) respectively[210]. The formation of these cyclopropanes is explained by the formation of phosphonium-substituted cyclopropanes (**341**) followed by expulsion of an alkyl halide moiety (equation 107). It is



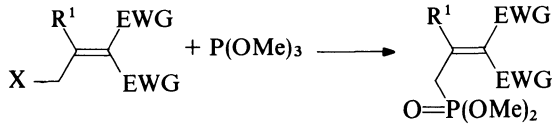
(107)



known that monoactivated allyl halides on reaction with trialkyl phosphites normally show the Arbuzov reaction with formation of phosphono-substituted electron-deficient olefins (**343**) (equation 108)[211–212]. Arbuzov reaction products (**344**) are formed during the reaction of double activated primary allyl halides with trialkyl phosphites when an alkyl or aryl function (R^1) substitutes the double bond (equation 108)[206]. The formation of the Arbuzov product is probably due to the steric hindrance which inhibits addition of the P-nucleophile across the double bond.



(342) (343)

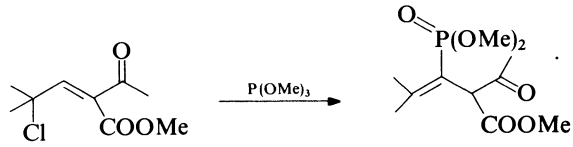


(108)

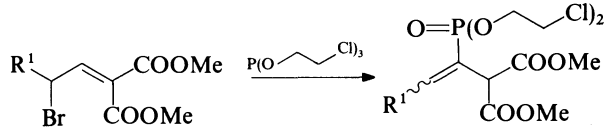
(291) (344)

R^1 = alkyl, aryl

In other cases, another pathway involving nucleophilic addition–elimination is observed giving rise to olefinic compounds **345**, **346** and **348**, although another route consisting of

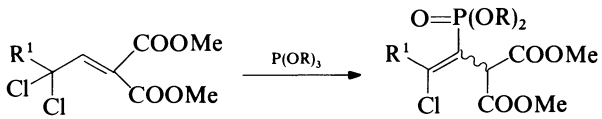


(299) (345)



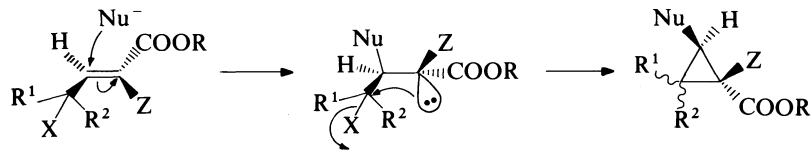
(109)

(291) (346)



(347) (348)

ring-opening of intermediate electrophilic cyclopropanes cannot be excluded (equation 109)[206]. In general the formation of the 2-substituted electrophilic cyclopropanes always takes place in a stereospecific way as outlined in equation 110.



(110)

The allyl halides geminally substituted with an ester and a cyano function, which exclusively occur in the (*E*)-configuration, give rise to cyclopropanes having the new substituent (Nu) *trans* with respect to COOR. Also a stereoisomeric mixture of 60% methyl (*E*)- and 40% methyl (*Z*)-2-acetyl-4-chloro-4-methyl-2-pentenoate affords a mixture consisting of 60% of the *trans* and 40% of the *cis* cyclopropane[191].

i. Kinetic study[191]. The kinetics of the latter cyclopropanation reactions have been studied in order to elucidate the reaction mechanisms. Therefore the rate of disappearance of the geminal alkyl signal and/or the olefinic proton in the allyl halides and the appearance of the corresponding alkyl signals and/or methine protons in the cyclopropanes were determined by ^{1}H-NMR spectrometry and the rate constants were calculated. The following conclusions can be drawn from all kinetic studies which are collected in Table 2. The reaction is of a second order, first order in allyl halide and first order in nucleophile. The rate constant for dimethyl 2-bromo-2-methylpropylidenemalonate with thiolate ions is very high while it is much lower in the case of methoxide, cyanide and phenoxide ions: $^-$SR $\gg$ $^-$OMe > $^-$CN > $^-$OPh. The rate-determining step is the Michael addition of the nucleophile to the double bond, followed by a fast intramolecular nucleophilic attack. Steric crowding is important as shown by the alkyl substitution pattern for the reaction with $^-$OMe: HC–alkyl $\gg$ C(Me)$_2$ > cyclohexyl > C(Me)(Et) > C(Et)$_2$. In addition the reaction rate is independent of the nature of the leaving group in the reaction of 2-bromo- and 2-chloro-2-methylpropylidenemalonate with methoxide $k_{Br} = k_{Cl}$. It is evident that the reactions are faster when the electrophilicity of the β-carbon atom is higher, i.e. when the substrates are activated by groups exerting stronger inductive and mesomeric effects: C(CN)$_2$ $\gg$ C(CN)COOMe > C(COOMe)COMe > C(COOMe)$_2$.

TABLE 2. Rate constants for the cyclopropanation reactions of electrophilic allyl halides **291** with nucleophiles at -5 °C[191]

R^1	R^2	X	Y	Z	Nu	k mol^{-1}·s^{-1}
Me	Me	Br	COOMe	COOMe	OMe	3.7×10^{-3}
Me	Me	Br	COOMe	COOMe	SBu-*t*	$> 10^2$
Me	Me	Br	COOMe	COOMe	SCH_2Ph	$> 10^2$
Me	Me	Br	COOMe	COOMe	SPh	1.0
Me	Me	Br	COOMe	COOMe	OPh	5.6×10^{-5}
Me	Me	Br	COOMe	COOMe	CN	2.2×10^{-4}
Et	H	Cl	COOMe	COOMe	OMe	~ 1
Me	Et	Br	COOMe	COOMe	OMe	5.2×10^{-4}
Et	Et	Br	COOMe	COOMe	OMe	5.3×10^{-5}
Cyclohexyl		Br	COOMe	COOMe	OMe	7.0×10^{-4}
Me	Me	Br	COOMe	CN	OMe	$> 10^2$
Me	Me	Br	CN	CN	OMe	$> 10^2$
Me	Me	Cl	COOMe	COMe	OMe	2.5×10^{-2}(*Z*)
Me	Me	Cl	COOMe	COMe	OMe	4.6×10^{-3}(*E*)
Me	Me	Cl	COOMe	COMe	SPr-*i*	$> 10^2$
Me	Me	Cl	COOMe	COOMe	OMe	3.7×10^{-3}

A rationale has been afforded to clarify the difference in reactivity of monoactivated allyl halides which normally give substitution products and diactivated allyl halides which normally afford cyclopropanes upon reaction with nucleophiles[213]. It is clear that the extent and the rate of formation of the MIRC product is dependent upon the enolate concentration and the rate constant for ring-closure, k_c, while the extent and the rate of

formation of the competing S_N2 product is dependent upon the concentration of the starting ester, the concentration of the nucleophile, and the rate constant for substitution, k_s (equation 111). Obviously, the relative concentrations of the starting ester, the

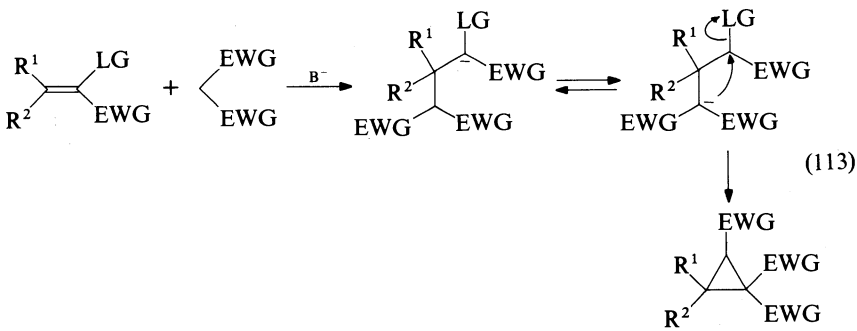
$$\begin{array}{l} S_N2 \text{ product} \xleftarrow[Nu^-]{k_s} X(CH_2)_nCH{=}CHCO_2R \\ \qquad\qquad\qquad\qquad\quad Nu^- \Big\uparrow\Big\downarrow k_{eq} \\ \qquad\qquad\qquad\qquad X(CH_2)_nCH(Nu)\bar{C}HCO_2R \xrightarrow{k_c} \text{MIRC product} \end{array} \tag{111}$$

nucleophile, and the enolate are related to the equilibrium constant, K_{eq}. To gain an appreciation for the factors which influence the magnitude of K_{eq}, one can use the thermodynamic cycle which is illustrated in equation 112. The individual steps associated

$$\begin{array}{ccc} Nu^- + H_2O + CH_2{=}CHCO_2R & \overset{\Delta G_t^\circ}{\rightleftharpoons} & NuCH_2\bar{C}HCO_2R + H_2O \\ \Big\uparrow\Big\downarrow \Delta G_1^\circ & & \Big\uparrow\Big\downarrow \Delta G_3^\circ \\ HO^- + NuH + CH_2{=}CHCO_2R & \overset{\Delta G_2^\circ}{\rightleftharpoons} & NuCH_2CH_2CO_2R + {}^-OH \end{array} \tag{112}$$

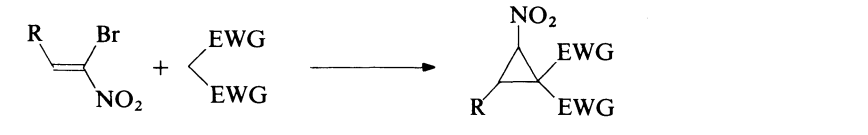
with the cycle include two acid–base equilibria (steps one and three) for which, at 25 °C, $\Delta G_1^\circ = -1.37\ \Delta pK_a$ and $\Delta G_3^\circ = -1.37\ \Delta pK'_a$, where $\Delta pK_a = pK_a(NuH) - pK_a(H_2O)$ and $\Delta pK'_a = pK_a(H_2O) - pK_a(R'CH_2CO_2R)$, while for step two, $\Delta G_2^\circ = [\Delta H^\circ(NuH) - \Delta H^\circ(NuC)] + [\Delta H^\circ(C{=}C) - \Delta H^\circ(CH)] - T\Delta S^\circ$. Thus, it follows that overall $\Delta G^\circ_{total} = \Delta G_t^\circ = \Sigma\,\Delta G_i^\circ = -1.37\ \ [pK_a(NuH) - pK_a(R'CH_2CO_2R)] + [[\Delta H^\circ(NuH) - \Delta H^\circ(NuC)] + [\Delta H^\circ(C{=}C) - \Delta H^\circ(CH)] - T\Delta S^\circ]$.

From these simple considerations, one can clearly see the role played by the pK_a difference between the conjugate acids of the nucleophile and the ester enolate on the position of the overall equilibrium. In doubly activated olefins the pK_a of the conjugate acid of the enolate resulting from the conjugate addition is substantially lower than that of the monoactivated system and ought to lead to a favourable shift in the equilibrium. Of course, shift of the equilibrium to the right does not guarantee the formation of a larger amount of the MIRC product, since changing from a less to a more highly stabilized enolate leads to a reduction in the rate of ring-closure, thereby still allowing the S_N2 process to compete favourably with the MIRC reaction.

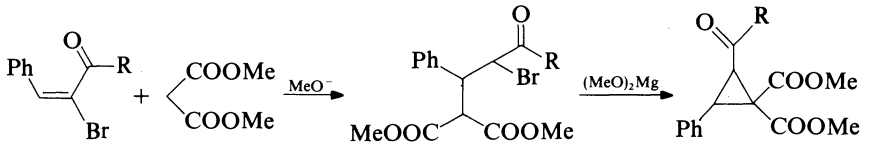


(113)

A particular case of a MIRC reaction is observed in substrates where the leaving group is situated in a geminal position to an electron-withdrawing function. Nucleophilic attack by an active methylene function gives a Michael addition product which undergoes ring-closure affording electrophilic cyclopropanes, substituted with three electron-withdrawing groups (equation 113)[398]. This general reaction scheme is illustrated by the following examples in equation 114.

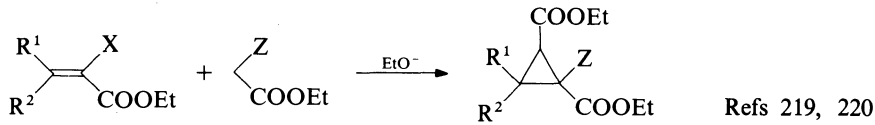


(349) EWG: COOR′, CN (350) Refs 214–217



(351) (352) (353, 83–95%)

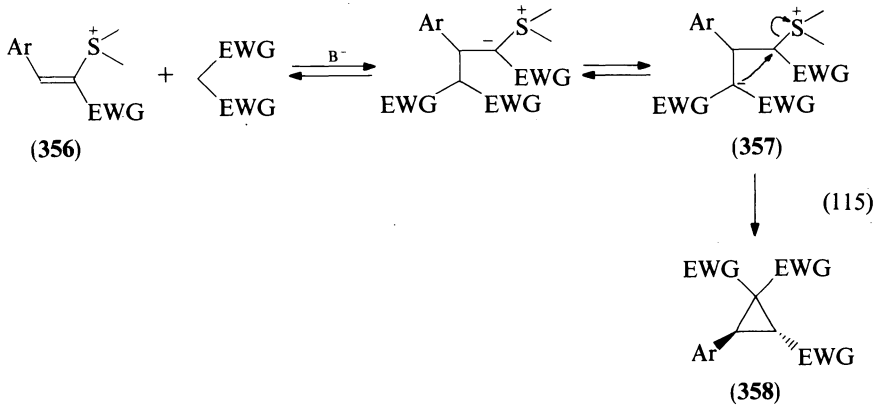
Ref. 218



(354) (355, $R^1 = R^2 = Me$, 64%) Refs 219, 220

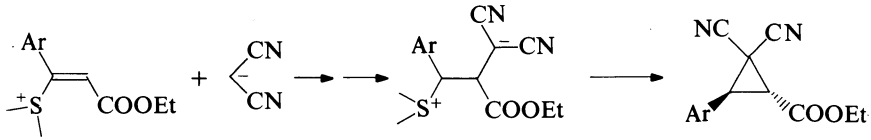
X = Cl, Br
Z = COOEt, CN (114)

The reaction of vinylsulphonium salts (**356**) with active methylene functions also gives electrophilic cyclopropanes via the formation of an unstable ylid which undergoes proton shift to an intermediate 1,4-sulphonium betaine (**375**) followed by expulsion of dimethyl sulphide (equation 115)[221,222]. In addition MIRC reactions of substrates with



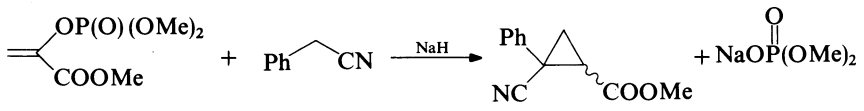
(356) (357) (115)

(358)



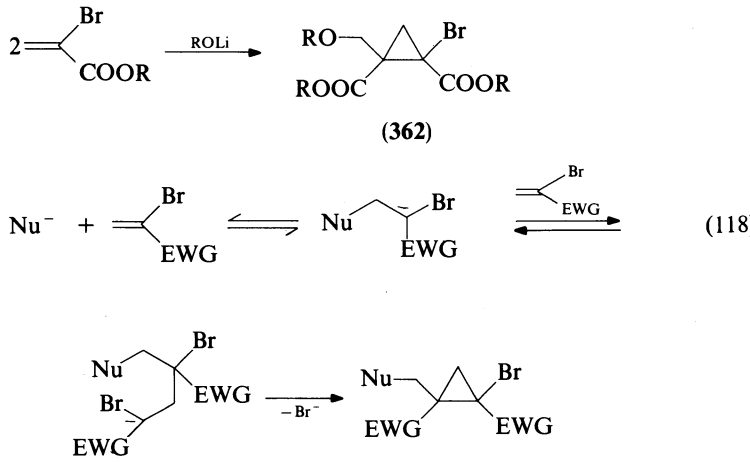
(359) (358a, 20–30%) (116)

the leaving group in the β-position give rise to the same electrophilic cyclopropanes (equation 116)[222,223]. Expulsion of a dimethyl phosphate ion in the ring-closure step also gives electrophilic cyclopropanes (**361**) (equation 117)[224]. Cyclopropanation via a double



(360) (361) (117)

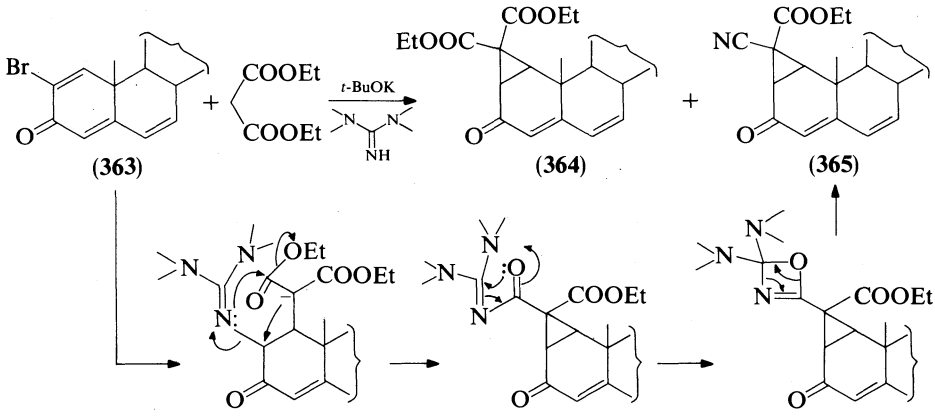
Michael addition takes place when 2-bromoacrylates are treated with nucleophiles[225]. The mechanism is given in equation 118.



(362)

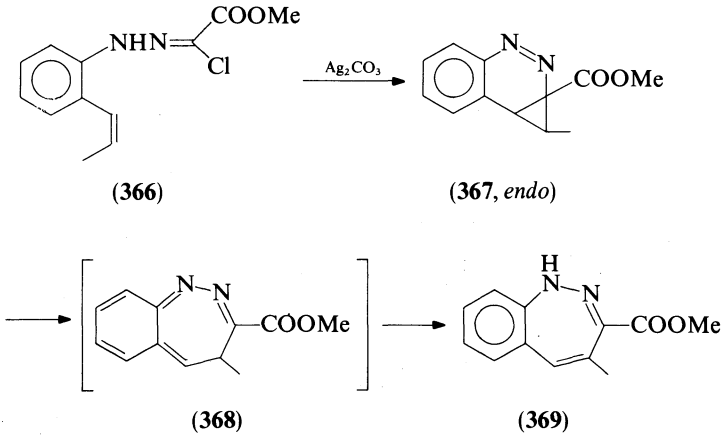
(118)

Cyclopropanation of steroids (**363**) at the 1,2-position with malonate in the presence of potassium *t*-butoxide and tetramethylguanidine takes place with formation of the di(alkoxycarbonyl)cyclopropane derivatives (**364**) accompanied by steroidal cyano-alkoxycarbonylcyclopropanes (**365**). When the reaction is carried without tetramethyl-guanidine only minor amounts of cyclopropyl steroids are isolated[226]. The formation of the cyano compound is explained by an initial nucleophilic displacement of bromine by the tetramethylguanidine moiety, followed by several steps (equation 119). Although the reaction of equation 120 cannot be classified as a MIRC reaction *sensu strictu* the formation of cyclopropa[c]cinnolines (**367**) via an intramolecular 1,1-cycloaddition of nitrilimines is mentioned here. Treatment of *o*-vinylphenyl-substituted chloroglyoxylate



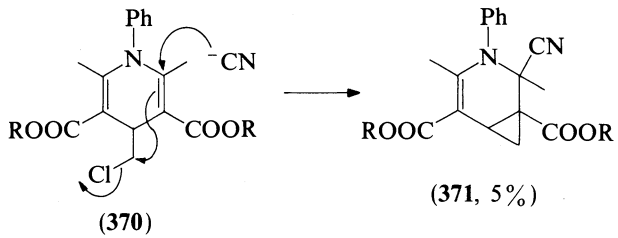
(119)

phenylhydrazones (**366**) with silver carbonate leads to nitrilimines. These reactive 1,3-dipoles undergo intramolecular 1,1-cycloaddition with complete retention of configuration to give cyclopropa[c]cinnolines (**367**). Thermolysis of these compounds results in the formation of benzodiazepines (**369**) (equation 120)[227]. A MIRC reaction is observed when



(120)

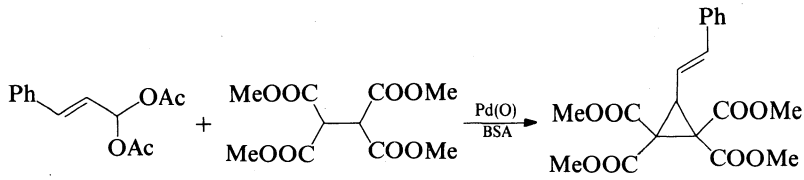
dihydropyridine (**370**) derivatives are treated with cyanide ion (equation 121)[228]. This reaction pathway has been used in the synthesis of tetracyclic methylene lactams[229].



(121)

d. Cyclopropanation via addition–nucleophilic substitution using non-activated olefins

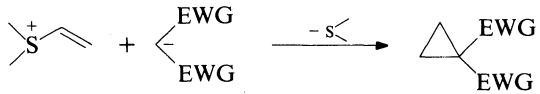
In a few cases addition of activated species bearing at least one electron-withdrawing group across non-activated olefins carrying a leaving group leads to the formation of electrophilic cyclopropanes. Reaction of the allylic geminal diacetate **372** with tetramethyl ethane-1,1,2,2-tetracarboxylate (**373**) in the presence of *O*, *N*-bis(trimethylsilyl)acetamide (BSA) and a Pd(0) catalyst (10 mol%) affords **374** (equation 122)[230].



(122)

(**372**) (**373**) (**374**, 65%)

Vinylsulphonium salts (**375**) are excellent precursors for the synthesis of electrophilic cyclopropanes via nucleophilic addition of active methylene functions followed by ring-closure (equation 123)[231,232]. A similar reaction is observed using butadienylsulphonium

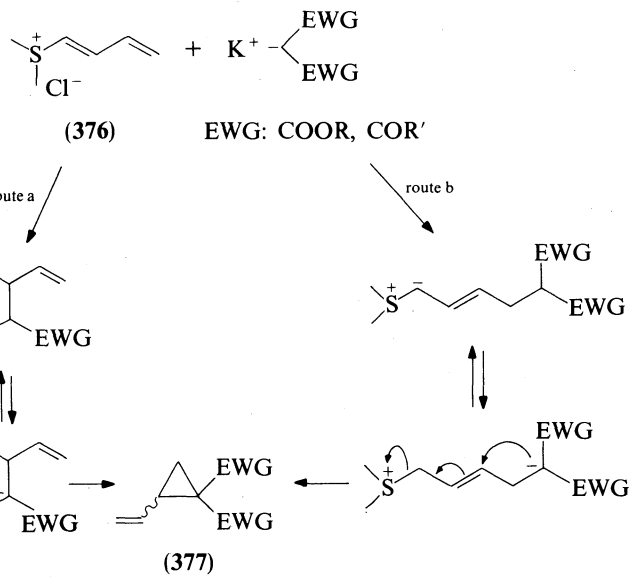


(123)

(**375**)

EWG: SO_2R (Refs 231, 233), COOEt, COR (Ref. 234)

salts (**376**) which give rise to electrophilic vinylcyclopropanes. This can be explained via two routes, either by addition at the 2-position or at the 4-position (equation 124)[235]. The

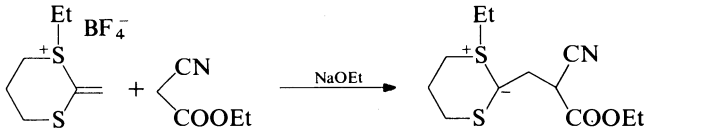


(124)

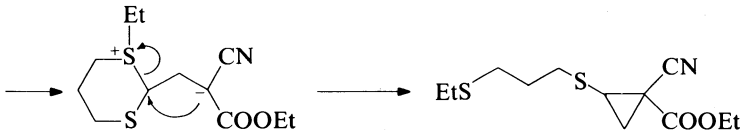
(**376**) EWG: COOR, COR′

(**377**)

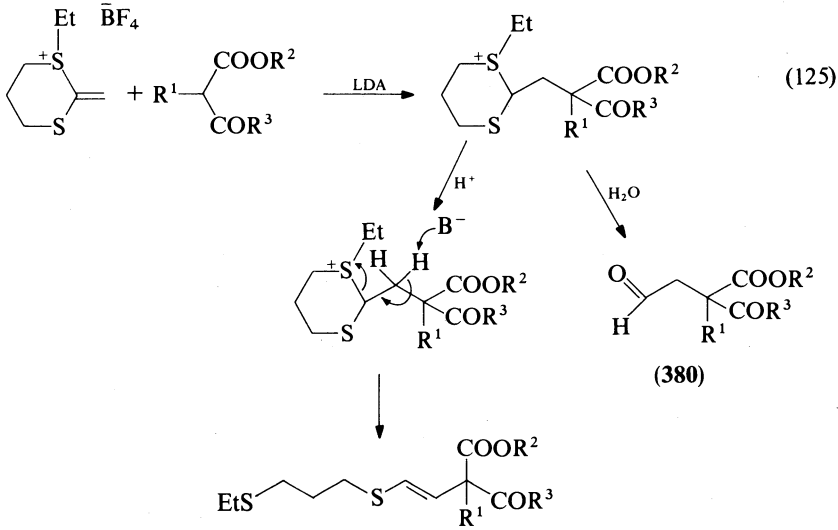
ketene thioacetal monosulphonium salt (**378**) reacts with ethyl cyanoacetate and a base with formation of an alkylthiocyclopropane derivative (**379**)[236]. However, reaction of the same sulphonium salt (**378**) with active methine compounds not containing CN in the presence of LDA does not give any cyclopropanation but a mixture of **381** and **380** is formed depending upon the workup conditions (equation 125)[236].



(**378**)



(**379**)



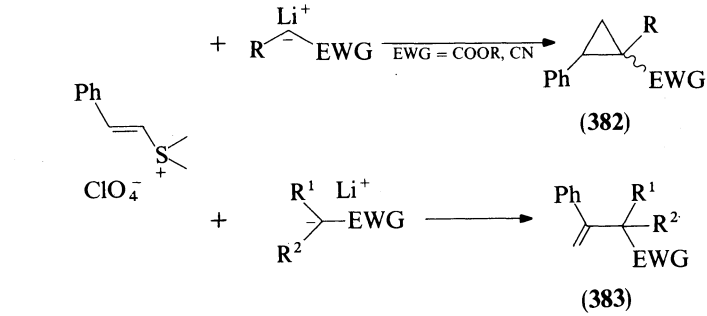
(125)

(**380**)

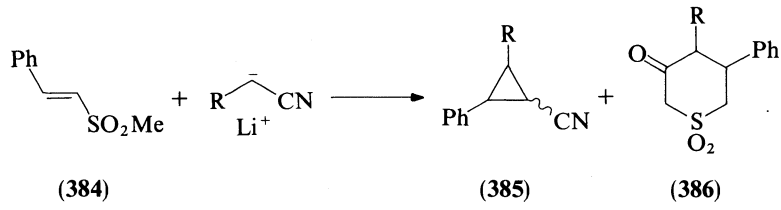
(**381**)

Reactions of dimethyl(vinyl)sulphonium salts with some lithium ester enolates and α-lithionitriles give cyclopropanes (**382**). When the lithium salts are tertiary, the butene derivatives (**383**) are formed (equation 126)[237].

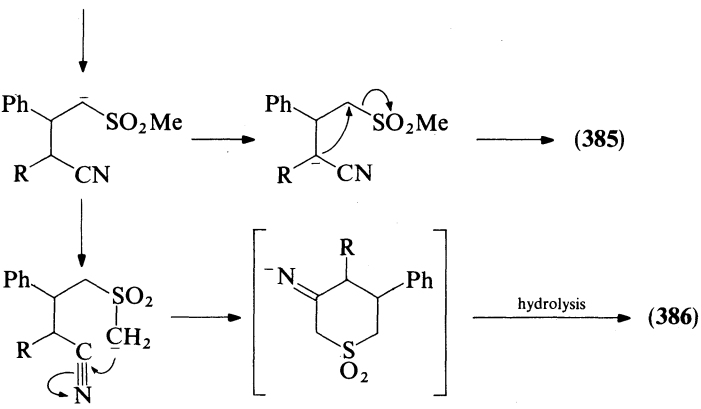
Vinyl sulphones (**384**) are subjected to nucleophilic addition by α-lithionitriles and give cyclopropanes (**385**) together with 3-oxothian-1,1-dioxides (**386**). The mechanism is given in equation 127[238]. It is remarkable that reaction of the sulphone with sodium



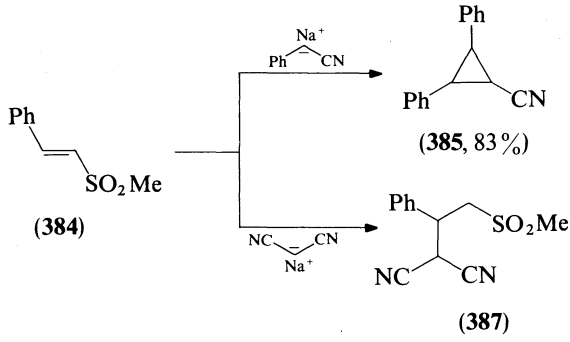
(126)



(127)



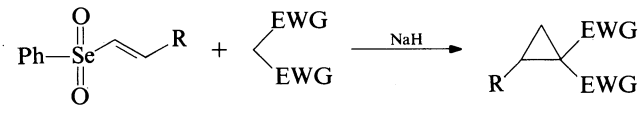
malononitrile only gives the addition product **387** while reaction with α-sodiophenylacetonitrile affords the cyclopropane **385** (equation 128). Consequently, the



(128)

cyclopropanation seems to be highly dependent on the nucleophilicity and/or stability of the carbanions[238].

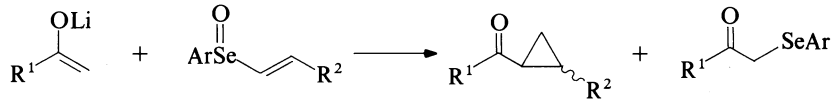
Treatment of vinylselenones (**388**) with active methylene compounds in basic medium also leads to the formation of electrophilic cyclopropanes (equation 129)[239,240].



(**388**) (50–90%) (129)

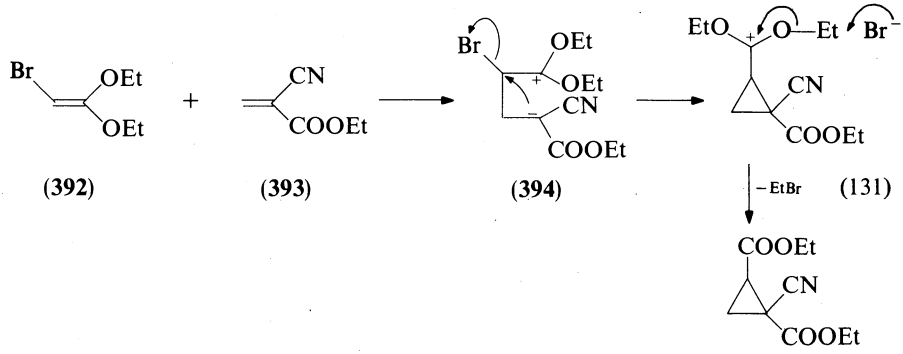
EWG: COOR, COR, $CONR_2$, CN

Cyclopropylcarbonyl compounds (**391**) are formed via a similar procedure during the reaction of enolate anions (**389**) with aryl vinyl selenoxides (**390**) (equation 130)[240].



(**389**) (**390**) (**391**, 75–90%) (130)

Cyclopropanation via the 3-halo-1,4-zwitterion **394** is observed when 1,1-diethoxy-2-bromoethylene (**392**) reacts with ethyl α-cyanoacrylate (**393**) to form diethyl 1-cyano-1,2-cyclopropanedicarboxylate (**395**). The initially formed zwitterion **394** undergoes intramolecular displacement of the bromide ion to form the dialkoxycarbenium ion, which in turn undergoes dealkylation to yield the cyclopropane **395** (equation 131)[241].



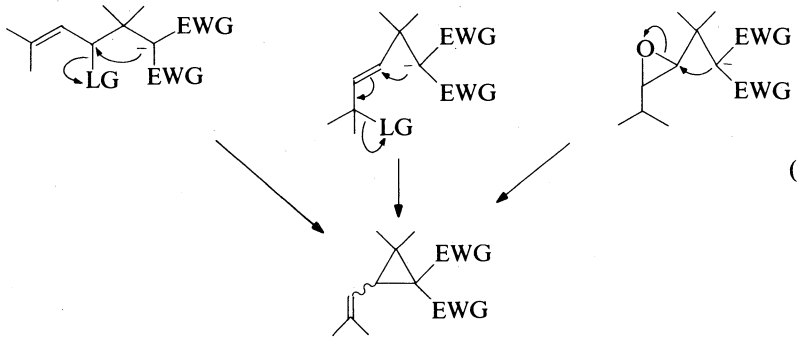
(**392**) (**393**) (**394**) (131)

(**395**, 50%)

B. Cyclopropanation via Nucleophilic Substitution Reactions

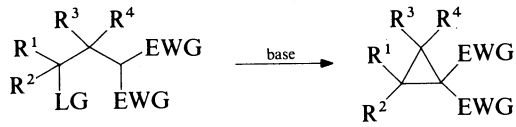
A large number of syntheses of electrophilic cyclopropanes carrying one or two electron-withdrawing groups have been performed based on an intramolecular S_N2 or S_N2' reaction. Synthetically equivalent to these two pathways is an epoxide-mediated ring-closure. These methods involve the generation of a carbanion in the α-position to one or two electron-withdrawing groups by the action of a base followed by the intramolecular

nucleophilic substitution. A general scheme illustrating the preparation of vinyl-substituted electrophilic cyclopropanes, important intermediates in the preparation of chrysanthemic acids, is presented in equation 132[242]. The first pathway especially is

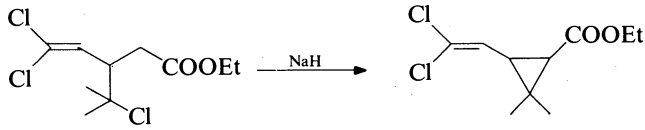


(132)

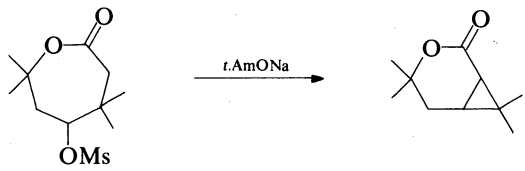
extremely well documented and a great variety of electrophilic cyclopropanes have been synthesized by equation 133. As activating groups, ester[243–247], ketone[248–250], sulphonate[251–252], cyanide[253], nitro[254], amide and thioamide[255] have been used (equation 134).



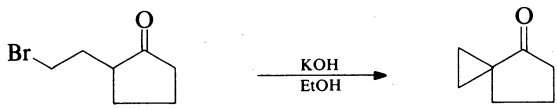
(133)



(**396**) (**397**, 60%) Ref. 245

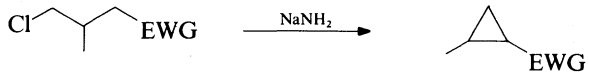


(**398**) (**399**, 95%) Ref. 256



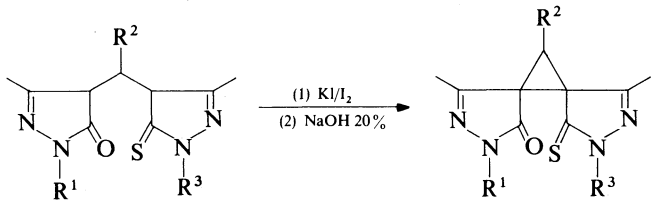
(**400**) (**401**, 27%) Ref. 250

(402) (403, 99%) Ref. 251



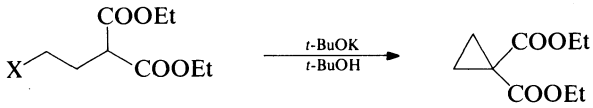
(134)

(404, EWG = CN)
(405, EWG = NO_2) (406) Refs 253, 254

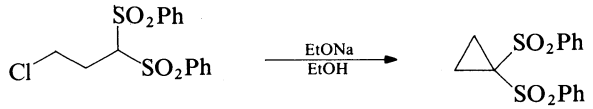


(407) (408) Ref. 255

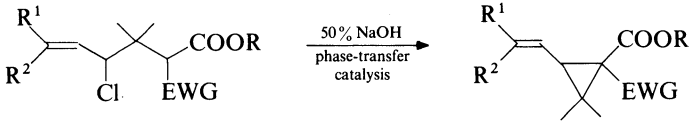
A series of electrophilic cyclopropanes geminally substituted with two electron-withdrawing groups have been synthesized by using an identical procedure. It is evident that the presence of two electron-withdrawing groups makes the ring-closure step easier than in cases where only one activating group is present[257, 258, 410]. Equation 135 illustrates this very efficient procedure with various examples.



(409) (410) Refs 42, 262

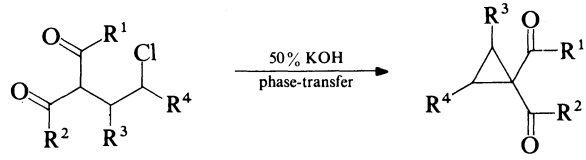


(411) (412) Ref. 258

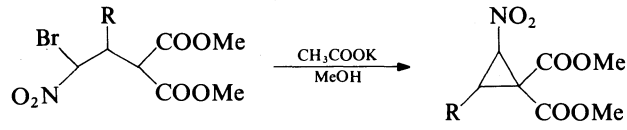


(413) (414) Ref. 259

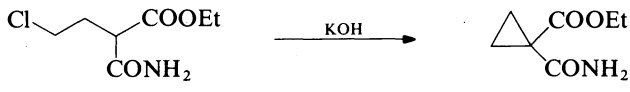
EWG: COOR, CN, COR



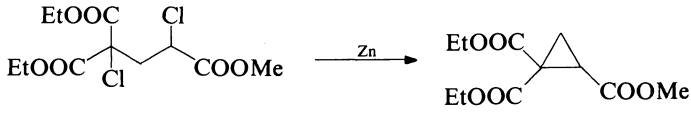
(415) (416) Ref. 261 (135)



(417) (417a) Ref. 260

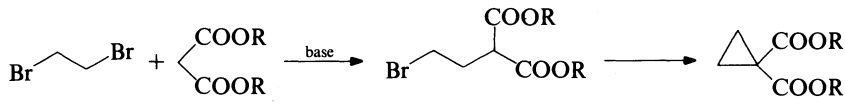


(418) (418a, 65%) Ref. 262



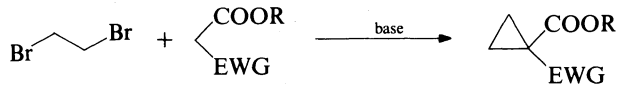
(419) (420) Ref. 263

A general procedure for the preparation of electrophilic cyclopropanes consists of treatment of 1,2-dibromoethane with active methylene functions. In fact the first synthesis of an electrophilic cyclopropane, namely diethyl cyclopropane 1,1-dicarboxylate (equation 136), was performed using this reaction by Perkin in 1885[1]. In this valuable method



(409) (410, 35–45%) (136)

the first step is a substitution reaction with formation of an intermediate γ-bromomalonate derivative which undergoes ring-closure. By this procedure a variety of electrophilic cyclopropanes have been prepared as shown in equation 137. However, the preparation of

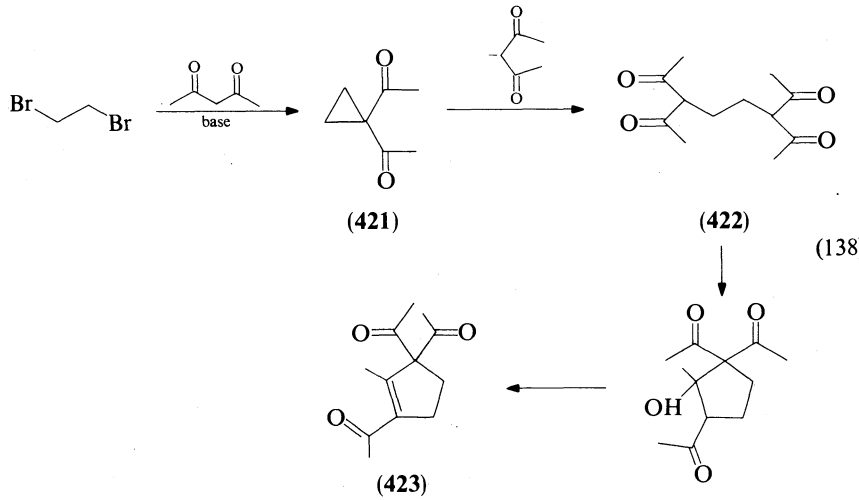


(137)

EWG:CN (Ref. 264)
EWG:SO_2Ph (Ref. 266)
EWG:COMe (Ref. 265)

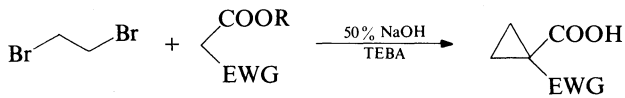
these electrophilic cyclopropanes has hitherto been accomplished in only poor yield[268, 316]. Furthermore, the inefficiency of this double alkylation necessitates a complicated separation of the cyclopropane from the active methylene functions.

In addition, condensation of 2,4-pentanedione with 1,2-dibromoethane only affords 1,1-diacetylcyclopropane (**421**) in 20% yield, together with 1,1,3-triacetyl-2-methyl-2-cyclopentene (**423**) formed via further attack of the 2,4-pentanedione carbanion on **421** and ring-closure of tetraacetylbutane (**422**) (equation 138)[269]. Better yields have been



(421) (422) (423) (138)

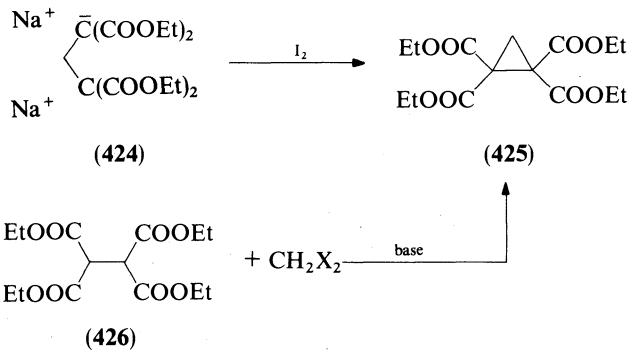
obtained using 50% NaOH–TEBA (equation 139), but in all cases saponification of the ester function takes place[270, 271].



(139)

EWG: COOR, CN, COMe

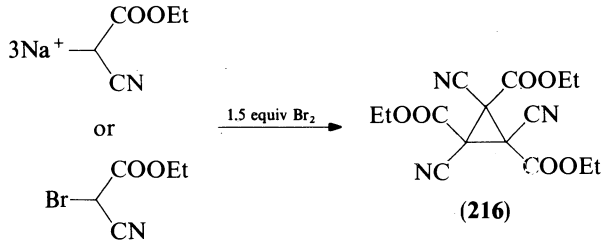
There are a number of related reactions; for example treatment of disodiotetraethylpropane-1,1,3,3-tetracarboxylate (**424**) with iodine[272] and the condensation of



(424) (425) (140)

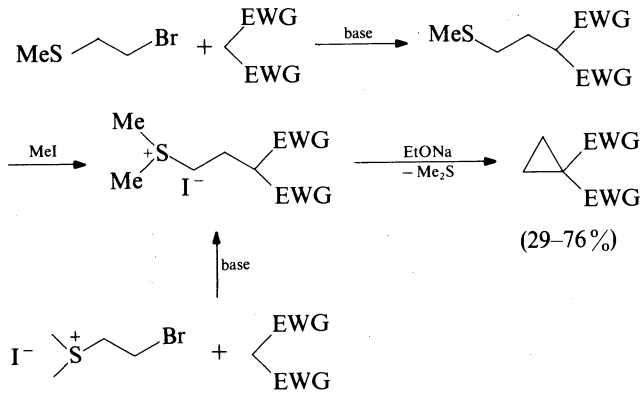
(426)

dibromo- or dichloromethane with tetraethyl ethane-1,1,2,2-tetracarboxylate (**426**) in the presence of a base give tetraethyl cyclopropane-1,1,2,2-tetracarboxylate (equation 140)[273]. The ester condensation of ethyl cyanoacetate in the presence of bromine or iodine or the brominated cyanoacetate gives rise to a cyclopropane substituted with six EWGs (equation 141)[274, 275].



(213) (216) (141)

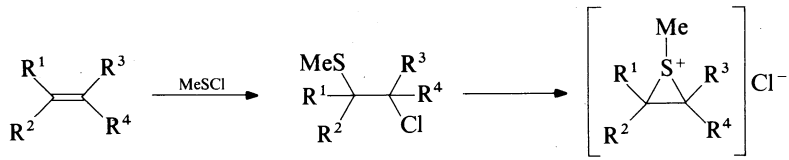
As observed in the examples above a variety of leaving groups, e.g. halogen atoms, tosyloxy and acyloxy functions, have been used. Another excellent procedure for the intramolecular ring-closure is the use of sulphonium salts with expulsion of dialkyl sulphide[276, 277] as shown in equation 142. An identical approach makes use of an



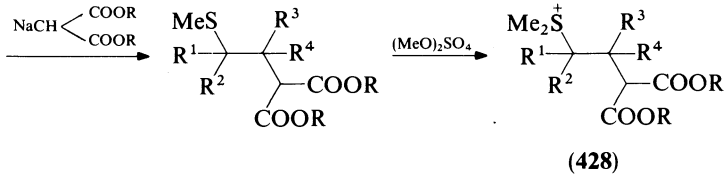
(142)

EWG: COOR, CN, PhCO, Ph

intermediate cyclic sulphonium salt, giving rise to highly substituted electrophilic cyclopropanes (equation 143)[278]. Unique procedures utilize the demercuration of 3,3-diacetylpropylmercuric chloride (**429**) yielding 1,1-diacetylcyclopropanes (**430**) (equation 144)[279].



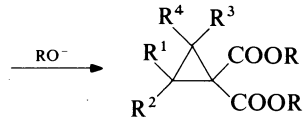
(427)



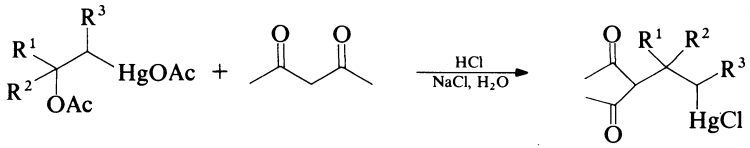
(428)

(143)

R^1, R^2: H, alkyl, ring residue
COOR, Ar
R^3, R^4: H, Me

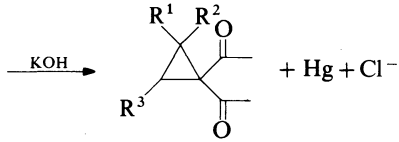


(143, R = Me: 52–74%)



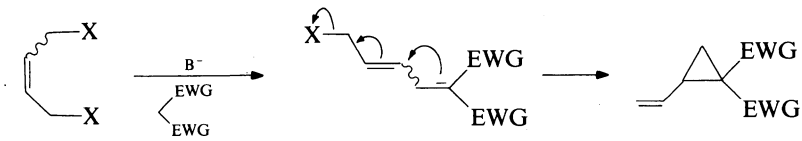
(429)

(144)



(430)

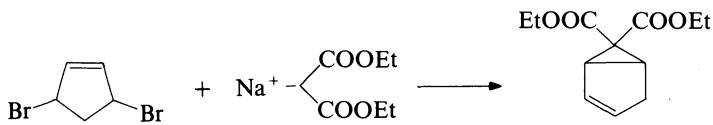
The S_N2' pathway for the preparation of electrophilic cyclopropanes is not well documented. The synthesis of 2-vinylcyclopropanecarboxylates (**432**) by reaction of 1,4-dihalo-2-butenes (**431**) with active methylene functions involves a S_N2' mechanism[280, 281]. In an analogous fashion, the reaction of 3,5-dibromocyclopentene (**433**) with diethyl sodiomalonate affords 6,6-diethoxycarbonylbicyclo[3.1.0]hex-2-ene (**434**)



(431) X = halogen

(432, EWG = COOR; 40–52%)

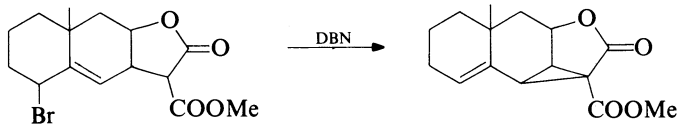
(145)



(433)

(434, 54%)

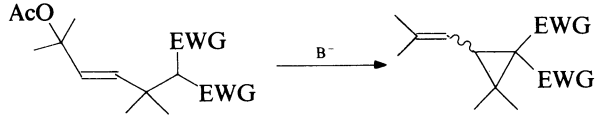
(equation 145)[281]. Treatment of the allylic bromide (**435**) with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in benzene solution results in a S_N2' displacement of bromide ion to generate the tetracyclic derivative **436** (equation 146)[282]. Cyclopropanation of functional-



(146)

(**435**) (**436**, 95%)

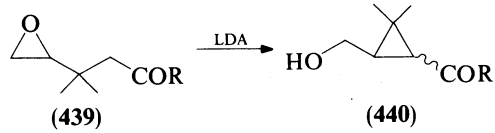
ized allylic acetates **437** in S_N2' fashion under basic conditions (LDA, NaH), readily occurs (equation 147) and some degree of stereoselectivity has been observed by the utilization of Pd complexes[283–285, 391]. Chrysanthemate analogues have been also synthesized by a similar procedure[286].



(147)

(**437**) (**438**, 65–90%)

Ring-opening of functionalized oxiranes (**439**) has been used in the synthesis of pyrethroid derivatives (**440**), but does not find any application in the preparation of doubly activated cyclopropanes (equation 148).



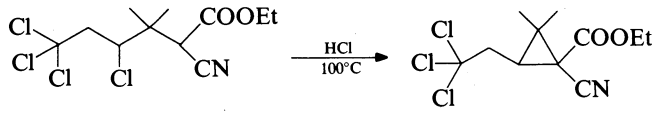
(148)

(**439**) (**440**)

R:OEt (Ref. 287)
R:N(Me)Ph (Ref. 242)

C. Miscellaneous Procedures for the Preparation of Electrophilic Cyclopropanes

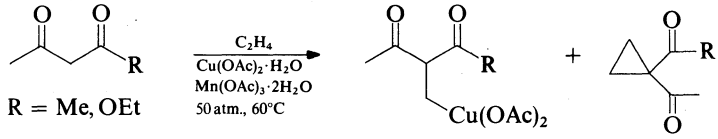
In addition to the general synthetic methods mentioned in the previous sections, this section deals with specific procedures for the synthesis of cyclopropanes which entail completely different reaction mechanisms. The acid-catalysed cyclization of the 4,6,6,6-tetrachlorohexanoic acid derivative **441** gives cyclopropanecarboxylic ester (**442**) (equation 149)[287].



(149)

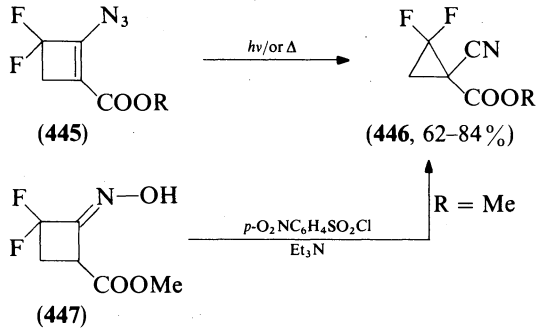
(**441**) (**442**)

Reactions of 2,4-pentanedione or ethyl acetoacetate with ethene in the presence of manganese(III) acetate and copper(II) acetate in an autoclave under 50 atm at 60 °C give a mixture of **443** and **444** (equation 150). This reaction involves an oxidative 1,3-cyclization of alkyl radicals[288].



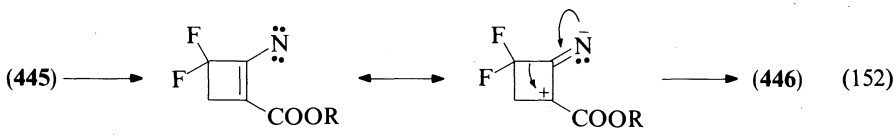
(443, ~ 20%) (444, ~ 20%) (150)

Thermally or photochemically induced ring contraction of 2-azido-3,3-difluorocyclobutenecarboxylates (**445**) leads to electrophilic 2,2-difluorocyclopropanes (**446**) (equation 151)[289]. Compound **446** (R = Me) is also accessible by base-catalysed



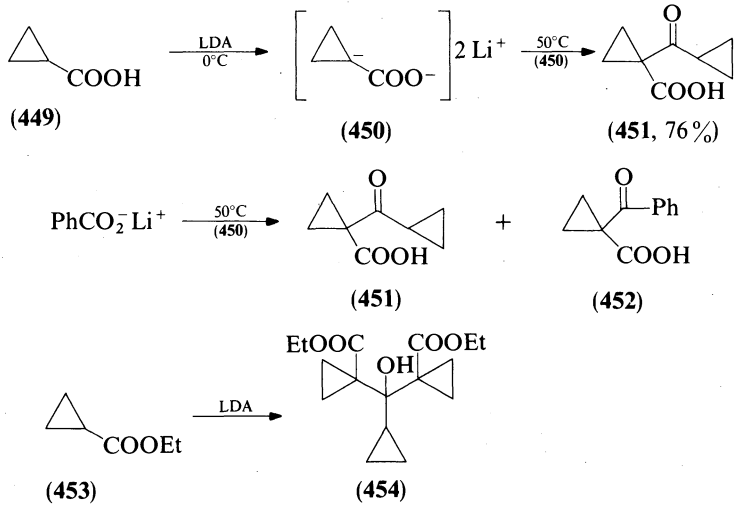
(445) (446, 62–84%) (447) (151)

elimination from the *O*-4-nitrobenzenesulphonate of the oxime (**447**). Both reactions are assumed to involve the formation of a nitrene species (**448**) (equation 152).



(445) (448) (446) (152)

Self-condensation of the dianion of cyclopropanecarboxylic acid (**450**) at 50 °C affords the electrophilic cyclopropane (**451**). Reaction of the dianion with other carboxylate salts,



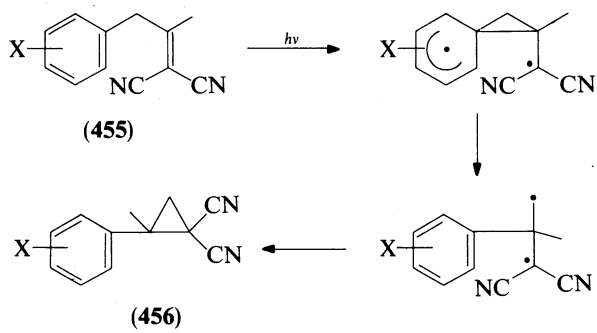
(449) (450) (451, 76%)

(451) (452) (153)

(453) (454)

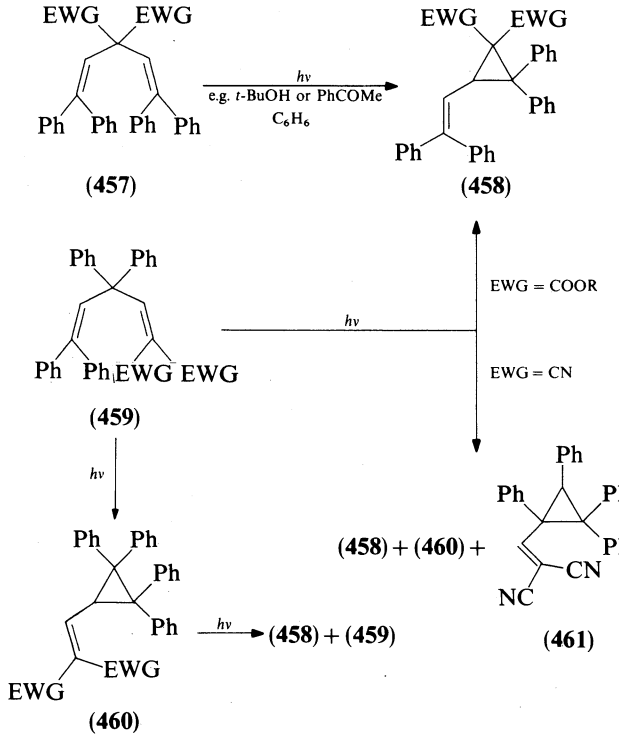
e.g. lithium benzoate, gives rise to both **451** and **452**[290]. However, self-condensation of the ethyl ester (**453**) only furnishes a trimeric diester alcohol (**454**) as the sole product (equation 153)[290–292].

Photochemical procedures for the preparation of electrophilic cyclopropanes are relatively important. Appropriately substituted electron-deficient olefins on photolysis undergo a di-π-methane rearrangement to give the corresponding cyclopropane derivatives. For example, 1,1-dicyano-2-methyl-3-arylpropenes (**455**) provide the dicyanocyclopropanes (**456**), presumably via the mechanism of equation 154[293, 294].



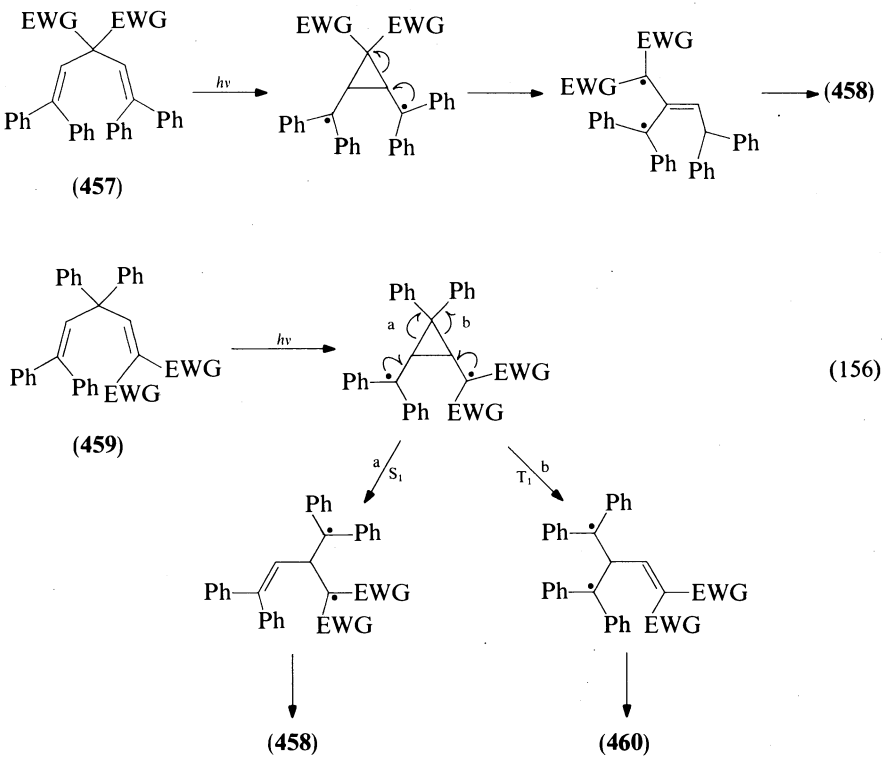
(154)

Electrophilic dienes **457** and **459** can also be converted into electrophilic cyclopropanes **458** and **460** via a di-π-methane rearrangement as illustrated by the examples of equation 155[295, 296]. The rearrangement of the dienes follows a typical di-π-methane



(155)

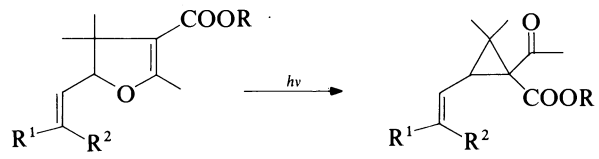
rearrangement as depicted in equation 156. Chrysanthemic acid derivatives have been prepared using a similar photochemical rearrangement starting from dienoates[297, 298].



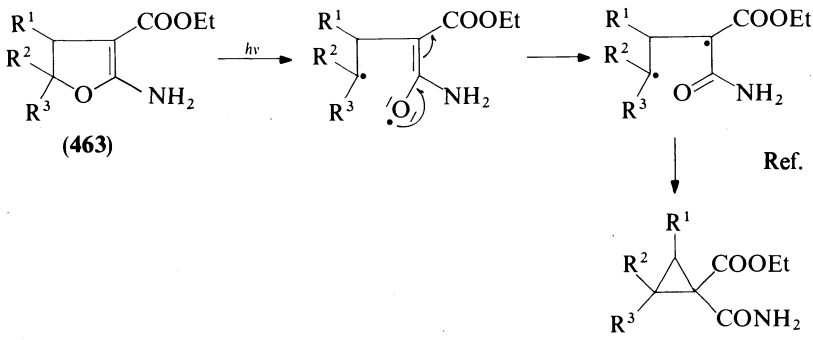
(156)

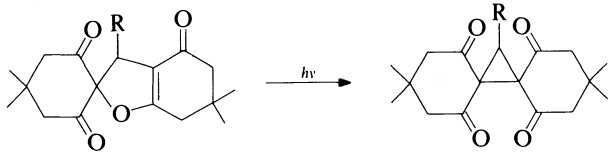
Photochemical rearrangement of dihydrofuran compounds **462** and **463** gives rise to the corresponding electrophilic cyclopropanes **414** and **464**[299, 300]. 1,1,2,2-Tetraacylcyclopropanes (**466**) have been prepared from the adducts of β-diketones and aldehydes (**465**) (equation 157)[301].

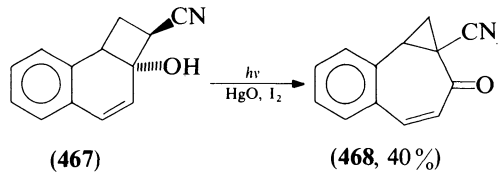
Irradiation of benzobicyclooctadienol (**467**) in benzene containing HgO and iodine gives a benzobicyclooctadienone (**468**) (equation 158). Its formation involves a rearrangement of an 8-membered C-centred radical generated by β-scission of an alkoxy radical (equation 158)[302].



(**462**) (**414**, EWG = COMe) Ref. 299







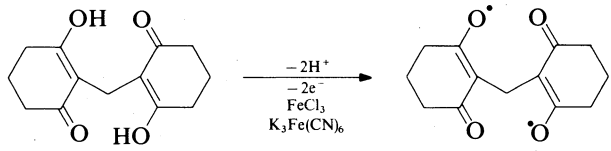
Methylene-bis-1,3-cyclohexanedione, on treatment with a solution containing equimolecular proportions of iron(III) chloride and potassium hexacyanoferrate(III), undergoes intramolecular carbon–oxygen and carbon–carbon coupling, giving a mixture of the isomeric dispirocyclopropane (**470**) and the dihydrofuran (**471**) (equation 159)[303].

An electrophilic cyclopropane of a completely different nature consists of carbethoxycyclopropyltriphenylphosphonium tetrafluoroborate (**475**). This compound has been prepared by reaction of cyclopropyltriphenylphosphonium bromide (**472**) with LDA. Treatment of the resulting ylide (**473**) with ethyl chloroformate and exchange of the counterion with sodium tetrafluoroborate provides the cyclopropane (equation 160)[357].

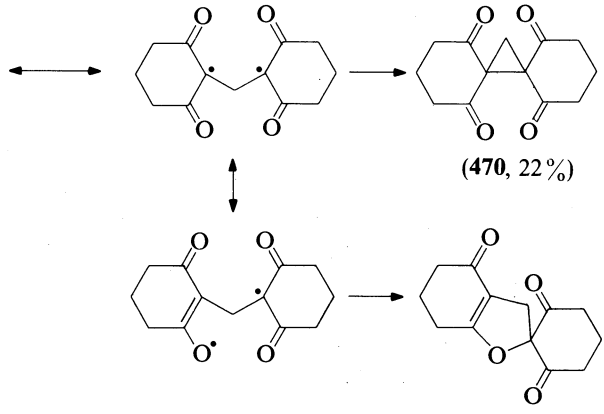
III. REACTIVITY OF ELECTROPHILIC CYCLOPROPANES

A. Introduction

Although electrophilic cyclopropane derivatives have been widely used in the synthesis of natural products especially in the total synthesis of polycarbocyclic sesquiterpenes[7,304], no systematic review describing the reactivity of electrophilic cyclopropanes (*sensu strictu*) towards various reagents has appeared. In addition to the excellent review of Danishefsky[7]



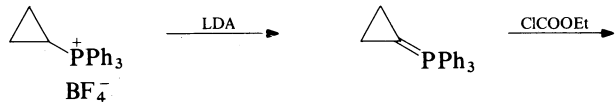
(469)



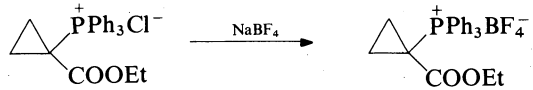
(470, 22%)

(471, 28%)

(159)



(472) (473)

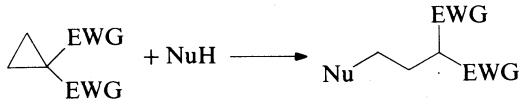


(474) (475, 80%)

(160)

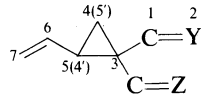
describing the use of electrophilic cyclopropanes in organic synthesis, two reviews dealing with organic syntheses via cyclopropanes have been published[6, 305]. In this section the reactivity of electrophilic cyclopropanes will be classified according to the reagents used and not to the reaction mechanisms observed during the various reactions. Applications of the observed reactions in total syntheses will also be mentioned in several cases.

The cyclopropane ring behaves in a manner analogous to that of an alkene linkage substituted on one carbon atom by one or two electron-withdrawing groups; ring cleavage occurs adjacent to the substituted carbon, and addition of the nucleophile leads to 1,1,3-trisubstituted propanes (equation 161). In contrast to double bonds, which are susceptible to Michael addition by virtue of one activating group, cyclopropanes require two such activating groups for homoconjugate addition in most cases. Recently, however,



(161)

ring cleavage of monoactivated cyclopropanes with nucleophiles have been observed using specific substrates. The latter reactions are treated elsewhere in this book. The terms 1,5 and 1,5′ have been suggested to signify alternate modes of homoconjugate additions and in cases of vinyl-substituted cyclopropanes the term 1,7 signifies vinylogous homoconjugate addition. The terms 1,4 and 1,6 are thus reserved for classical Michael reactions (cf. structure **475a**)[306].

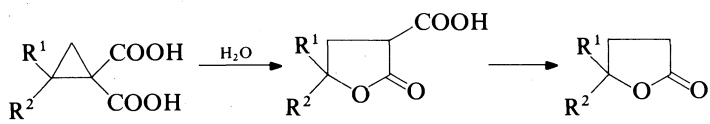


(475a)

B. Reaction of Electrophilic Cyclopropanes with Nucleophiles and Bases

1. Reaction of electrophilic cyclopropanes with oxygen nucleophiles and bases

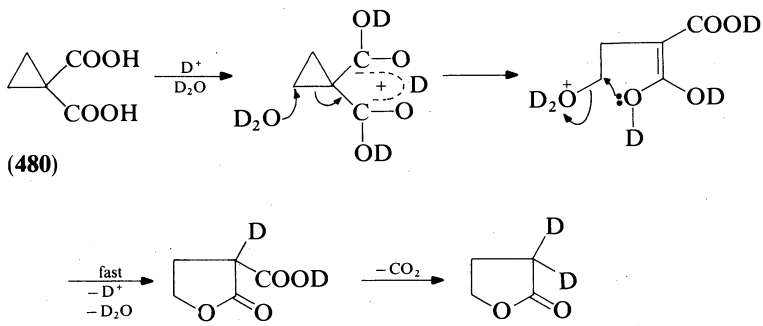
Heating of 1,1-cyclopropanedicarboxylic acids (**476**) in water results in a rearrangement with formation of γ-butyrolactonecarboxylic acids (**477**) which subsequently decarboxylate to the corresponding butyrolactone (**478**) (equation 162)[307, 308]. The reaction also



(162)

(476) **(477)** **(478)**

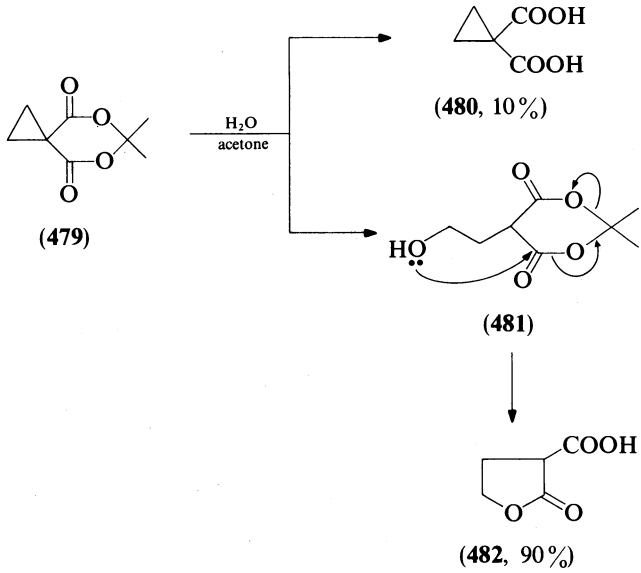
takes place in aqueous sulphuric acid. The rate-determining step of the isomerization reaction is believed to be a nucleophilic attack of water on a ring-carbon atom of protonated 1,1-cyclopropanedicarboxylic acid which is followed by a rapid ring-closure of the 3-hydroxypropane-1,1-dicarboxylic acid into the lactone as shown in experiments carried out in D_2O (equation 163). The ratio of the isomerization rates is 1/31/81 000 for



(480)

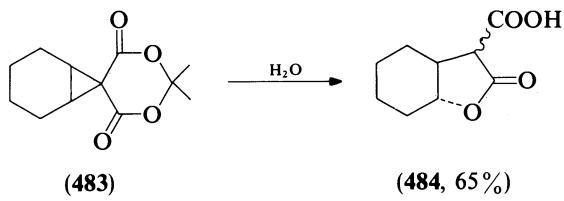
(163)

compounds **476** ($R^1 = R^2 = H$; $R^1 = H$, $R^2 = Me$ and $R^1 = R^2 = Me$), respectively. When the spiro-activated cyclopropane (**479**) is heated with aqueous acetone a 9:1 mixture of the lactone (**482**) and the dicarboxylic acid (**480**) is obtained. Thus, with water as a nucleophile, ring cleavage is faster than acylal cleavage. Presumably, the spiroacylal functions as an active ester in the cyclization of the initially formed 1,5-adduct (**481**) (equation 164)[309].



(164)

The stereochemical course of the ring-opening has been shown to involve inversion of configuration by water by studying the solvolysis of spiroacylal (**483**) (equation 165)[309].

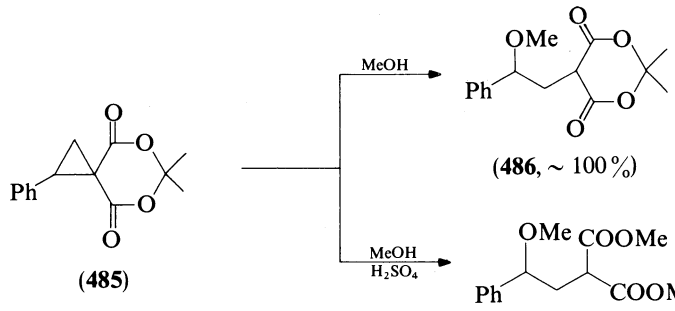


(165)

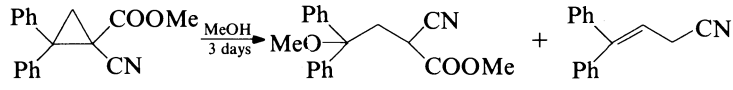
Solvolysis of electrophilic cyclopropanes with alcohols and phenols readily occurs as illustrated by the following examples of equations 166–168. It is worthwhile to note that methanolysis at 126 °C of (+)-(*E*) methyl 1-cyano-2-phenylcyclopropanecarboxylate (**495**) gives rise to (−)-(*S*)-methyl 2-cyano-4-methoxy-4-phenylbutanoate (**496**), indicating that the nucleophilic substitution reaction at the benzylic carbon of the cyclopropane proceeds with essentially complete inversion of configuration (equation 169)[312].

2-Methoxycyclopropanes (**498**) undergo ring cleavage with methanol when one of the electron-withdrawing groups is a cyano (equation 170)[192].

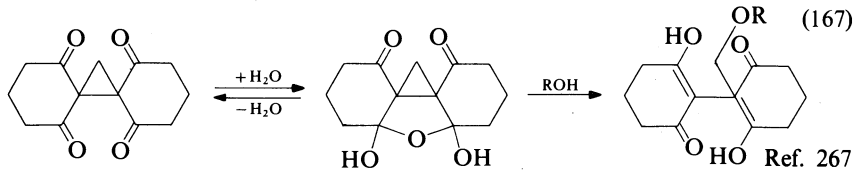
Few reports deal with the reactivity of alkoxides and phenoxides with electrophilic cyclopropanes. Treatment of the cyclopropane-1,1-dicarboxylate (**500**) with sodium



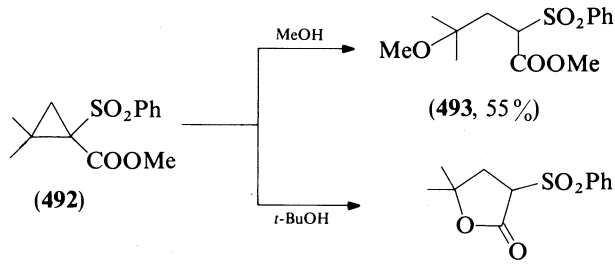
(485) (486, ~ 100%) (487, 85%) (166) Ref. 310



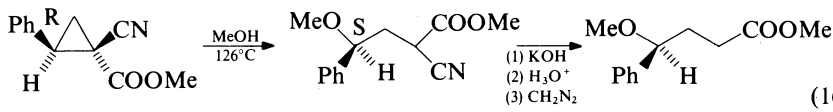
(488) (489) (490) Ref. 311



(470) (491, 80–83%) (167) Ref. 267

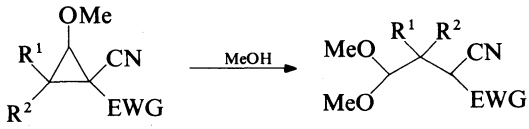


(492) (493, 55%) (494, 5%) (168) Ref. 311



(+)-(*E*) (−)-(*S*) (−)-(*S*) (169)

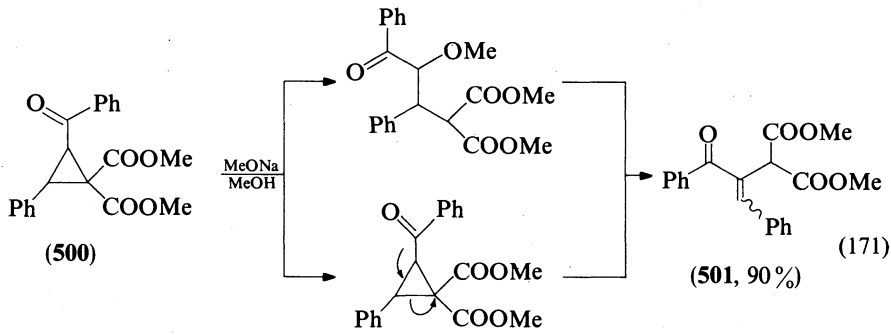
(495) (496, 86%) (497)



(498) (499, 80–95%) (170)

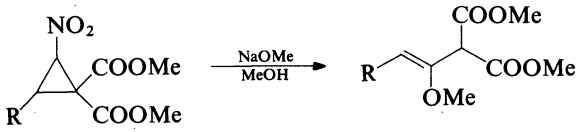
EWG = COOMe, COMe, CN

methoxide in methanol results in the formation of an isomeric α,β-unsaturated carbonyl compound (**501**). The formation of the latter compound could either be explained by an addition reaction with ring-opening followed by elimination of methanol or by proton abstraction followed by a conjugate shift of electrons (equation 171)[313]. However, reaction



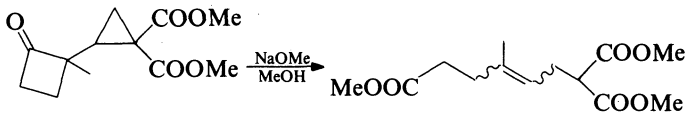
(500) (501, 90%) (171)

of the nitrocyclopropane (**417**) with sodium methoxide results in the formation of enol ether (**502**) (equation 172)[404].



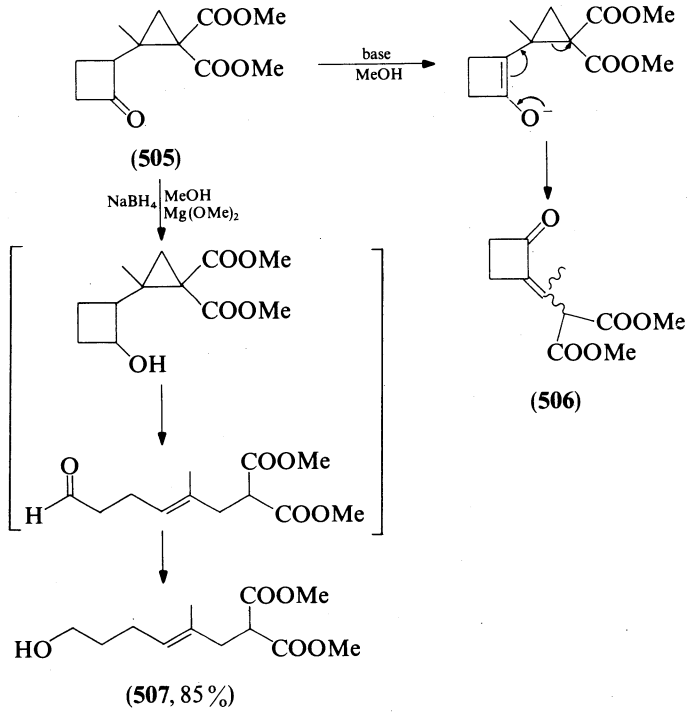
(417) (502, 31–89%) (172)

A completely different fragmentation pattern giving **504** is observed when the cyclopropane **503** is treated with sodium methoxide in methanol (equation 173). However,



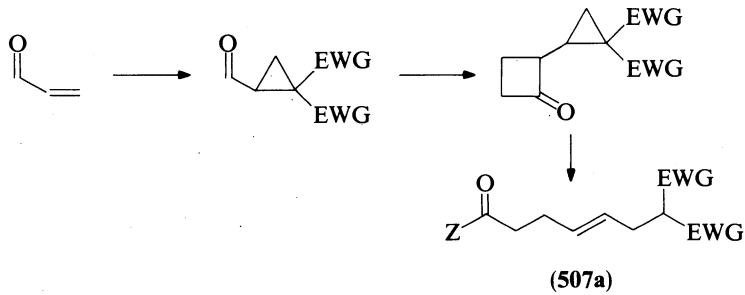
(503) (504, 80–84%) (173)

treatment of the isomeric compound **505** with methanolic base led to elimination via the enolate rather than fragmentation. *In situ* reduction of the ketone (**505**) with sodium borohydride during the reaction with magnesium methoxide provides the ring-opened product **507** (equation 174). This reaction sequence represents a double chain extension of



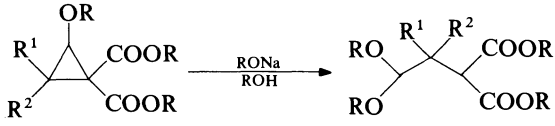
(174)

an α,β-unsaturated carbonyl system and has found application in the synthesis of many acyclic terpene units (equation 175)[314].

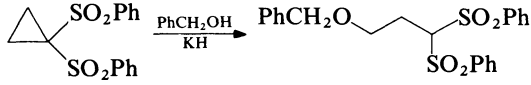


(175)

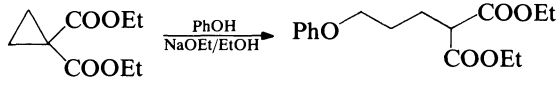
Ring-opened products **295**, **508** and **509** substituted with the attacking nucleophile, are formed on treatment of the methoxycyclopropane-1,1-dicarboxylates (**294**) and 1,1-bis(benzenesulphonyl)cyclopropane (**412**) with alkoxides and of cyclopropane 1,1-dicarboxylate (**410**) with phenolate. The presence of base is necessary to induce ring cleavage in the alkoxy-substituted dicarboxylates. Reaction of **294** (R^1, R^2 = H) with methanol does not lead to ring-opening at all (equation 176). Intramolecular *O*-alkylation of β-keto ester enolates (derived from **510** and **512**) by activated cyclopropanes provides a pathway to tetrahydrofurylidene derivatives (**511**) and dihydrofurans (**513**) (equation 177)[317]. Ring-opening of electrophilic cyclopropane derivatives **514**, **516** and **518**



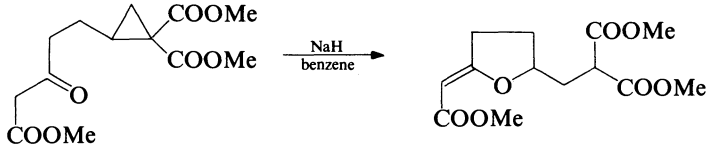
(294) (295, 75–90%) Ref. 192



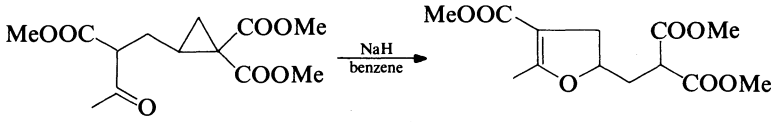
(412) (508, 60%) Ref. 315 (176)



(410) (509, 60%) Ref. 316



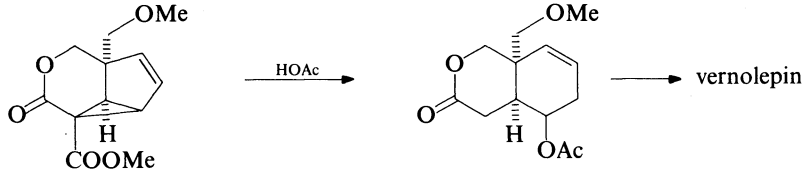
(510) (511, 49%) (177)



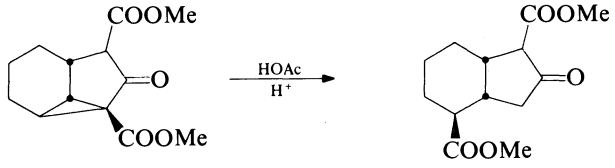
(512) (513, 74%)

with acetic acid and a trace of sulphuric acid have been used in the synthesis of sesquiterpene lactones[96], iridoids[318] and prostaglandins (equation 178)[319, 320].

Reaction of the spirocyclopropane (**470**) with formic or acetic acid results in ring-opening with simultaneous cyclopropanone formation, followed by addition of the acid

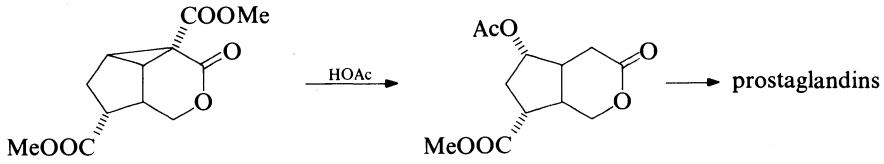


(514) (515, 79%) Ref. 96

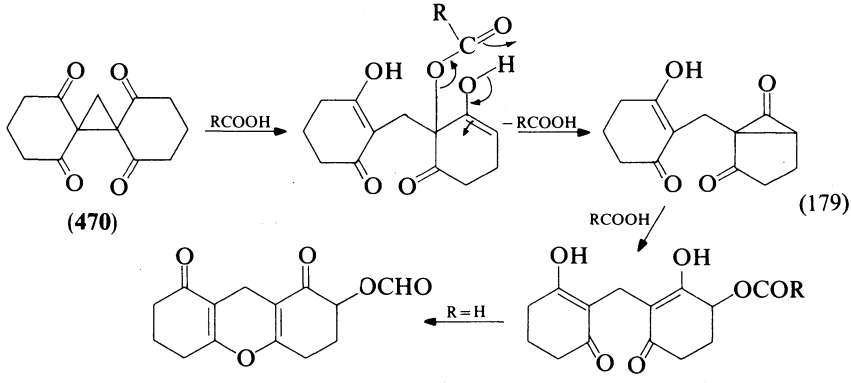


(178)

(516) (517, 74%) Ref. 318



(518) (519, 90%) Refs 319, 320

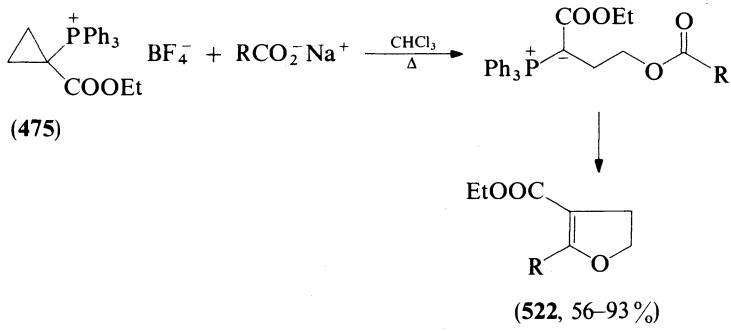


(179)

(470)

(521, 38%) (520, R = Me: 54%)

with formation of **520** or **521** (equation 179)[354].The reaction of carbethoxycyclopropyltriphenylphosphonium tetrafluoroborate (**475**) with carboxylic acid salts gives 5-substituted-4-carbethoxy-2,3-dihydrofurans (**522**). The reaction proceeds via attack of the carboxylate anion on the geminally activated cyclopropane to give an intermediate ylid



(180)

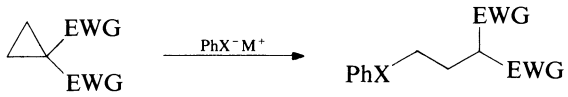
(475)

(522, 56–93%)

followed by an intramolecular Wittig reaction at the resulting ester carbonyl group (equation 180)[321].

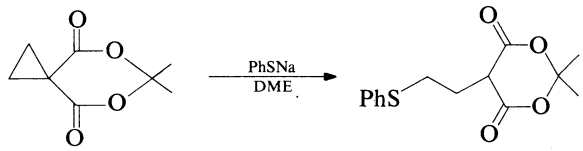
2. *Reaction of electrophilic cyclopropanes with sulphur and selenium nucleophiles*

The reactivity of electrophilic cyclopropanes towards S- and Se-nucleophiles shows great resemblance to the reaction with O-nucleophiles. Treatment of the cyclopropanes with thiophenolates or selenolates results in ring-opening (equation 181). The reaction of



EWG = COOEt; X = S: Ref. 316 (54%)
EWG = COOEt; X = Se: Ref. 322
EWG = SO_2Ph; X = S: Ref. 315

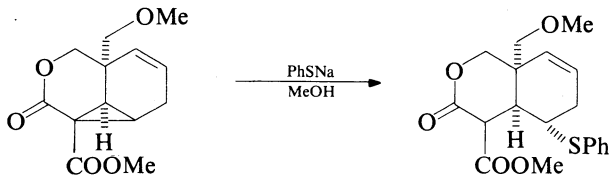
(181)



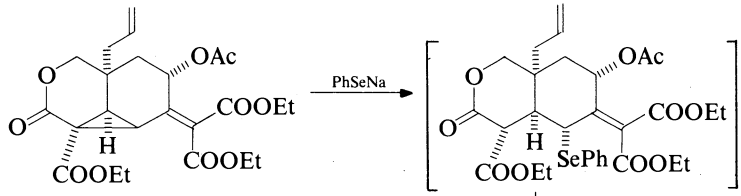
85% Ref. 329

the spiro compounds runs very smoothly while similar reactions for other electrophilic cyclopropanes could be achieved only at higher temperatures in a relatively inefficient fashion[329]. This ring-opening is one of the key steps in the preparation of vernolepin[96, 323] and prostaglandins (equation 182)[324, 325]. It is worthwhile to note that in the last reaction the ring-opening only proceeds in a 1,5 sense and not in a 1,7 sense. The latter observation is in contrast with the reaction of the vinylcyclopropane **528** with thiols in the presence of sodium alkoxide as a catalyst where a mixture of the 1,5- and 1,7-addition (**529** and **530** respectively) is formed (equation 183). Ring-opening with thiols without alkoxides results in the formation of only the 1,7-addition product[326].

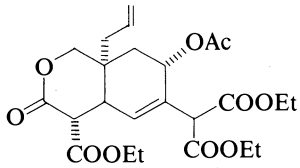
Reinvestigation of the reaction of butanethiol with vinylcyclopropane (**528**) showed a mixture of the 1,7-adduct (**531**) and of **532** in nearly equal amounts[332a]. One scheme for the formation of **531** and **532** entails attack by a butanethiyl radical at the terminus of the alkene with concurrent ring-opening to afford a malonyl radical. The latter could abstract hydrogen from the thiol to give **531** or cause a radical opening of another cyclopropane to give a new radical which upon hydrogen abstraction would produce **532** (equation 184).



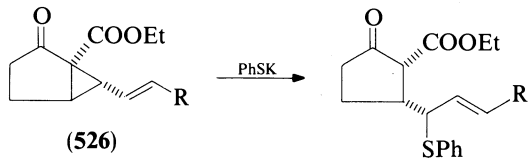
(**514**) (**523**, 80%) Ref. 96



(524)

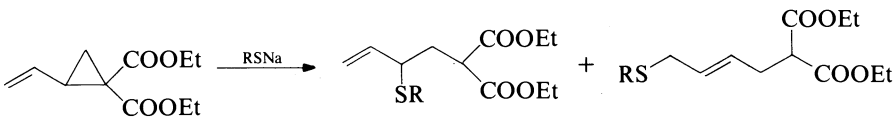


(525) (182) Ref. 323

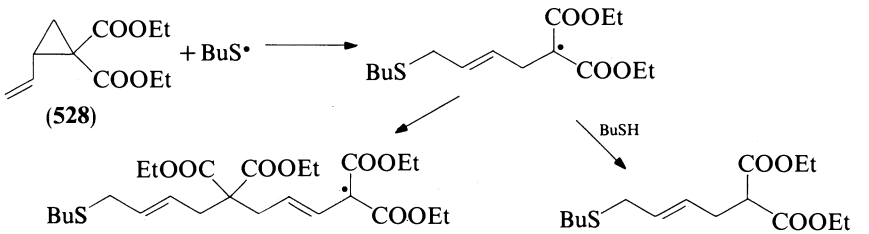


(526)

(527, R = Ph: 69%)



(528) (529) (530) (183)

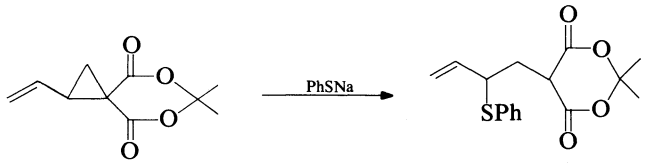


(528) (531) (184)

(532)

Carrying out the reaction under different reaction conditions (solvent, mercaptide concentration, presence of elemental sulphur) gives rise to variable ratios of reaction products. These results are interpreted in terms of competing 1,7-diradical and 1,5-nucleophilic pathways. The former is reduced in importance relatively to the latter on increasing the mercaptide concentration[332a].

However, ring cleavage of the spiro compound **533** only occurs in a 1,5 sense and gives **534** (equation 185)[327]. The effect of spiro activation in promoting 1,5-addition to the

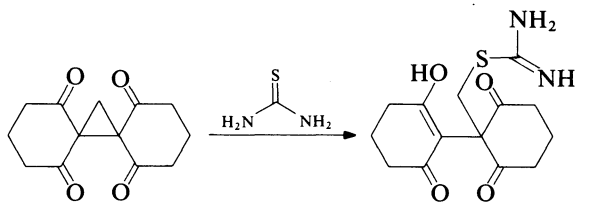


(185)

(**533**) (**534**, 100%)

exclusion of the 1,7 mode may be a consequence of specific structural features of the system. Alternatively it may arise from the mild reaction conditions which suffice for the spiro-activated vinylcyclopropane.

Finally, addition of thiourea to the spirocyclopropane (**470**) results in ring-opening with formation of **535** (equation 186)[328]. In contrast to the 2-methoxy-substituted cyclopropanes, the thio-substituted products do not show any ring-opening on treatment with



(186)

(**470**) (**535**, 73%)

thiolates. Except when R^1 or R^2 is an hydrogen atom, only minor amounts of thioacetals are formed[192].

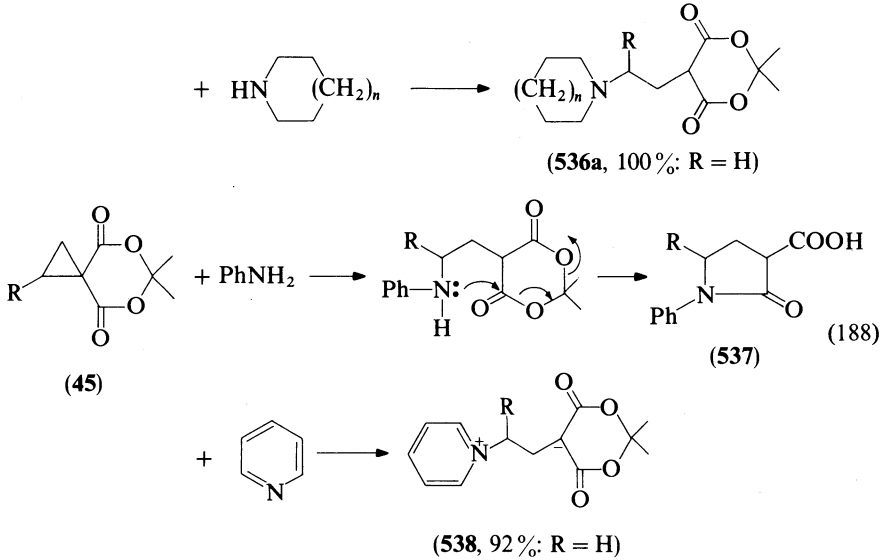
3. Reaction of electrophilic cyclopropanes with nitrogen nucleophiles

The reaction products formed during the reaction of electrophilic cyclopropanes with amines are strongly dependent upon the substitution pattern and the nature of the amines. Treatment of unsubstituted cyclopropane 1,1-dicarboxylates (**410**) with secondary amines gives rise to the normal ring-opened compounds (**536**) (equation 187), while reaction with primary amines does not result in any ring-opening. Instead, preferential attack of the amine at ester groups occurs, leading to *N*-substituted amides with retention of the cyclopropane ring[316].

(187)

(**410**) (**536**, 40–75%)

Spiro compound **45** reacts with secondary cyclic amines to produce **536a** (equation 188). On the other hand the spiro compound **45** in reaction with aniline gives a lactam (**537**) via sequential 1,5-addition and internal acylation[329]. Even the weakly nucleophilic pyridine reacts with **45** to give the betaïne **538** (equation 188)[329, 330].

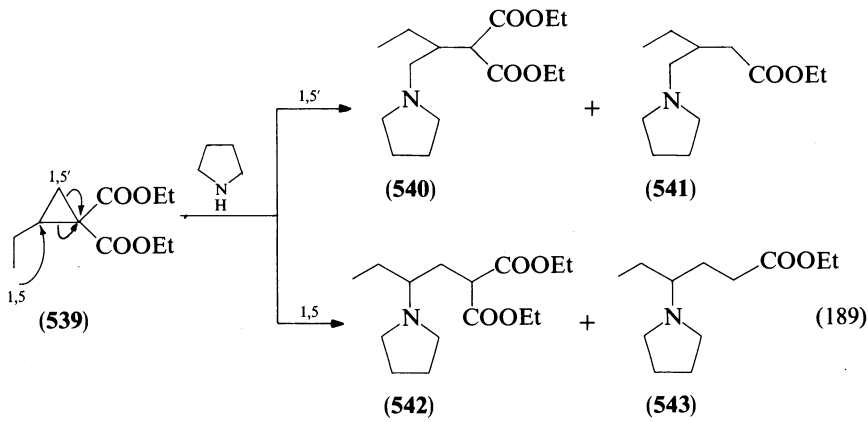


(**536a**, 100%: R = H)

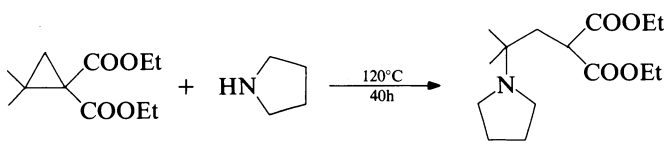
(**45**) (**537**) (188)

(**538**, 92%: R = H)

On reaction with pyrrolidine the 2-ethylcyclopropane **539** provides a mixture of four compounds (**540**, **541**, **542** and **543**) arising from a 1,5- and 1,5′-attack in a ratio of 2.5 : 1,



(**539**) (**540**) (**541**) (**542**) (**543**) (189)



(**544**) (**545**, 13%)

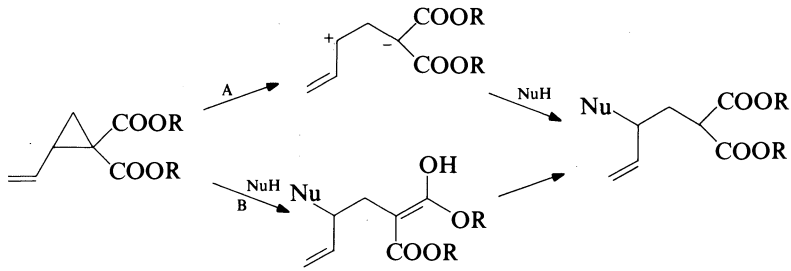
while the tertiary compound **544** gives rise to **545** in a very slow reaction and low yield (equation 189)[331]. In sharp contrast with the ethyl derivative **539**, reaction of the spiro-activated compound **45** with amines leads to exclusive attack at the more substituted carbon. Thus, the spiro acylal linkage may confer greater charge separation in the transition state for ring-opening, thereby favouring, more strongly, attack at the most substituted carbon[329].

Reaction of the vinyl-substituted compound **528** with secondary amines results in an exclusive 1,5-addition (equation 190)[326, 331]. Danishefsky suggested that the preponder-

(190)

(528) **(546**, 35–70%)

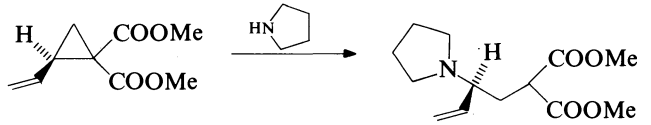
ance of the 1,5-pathway can be related to the prevalence of S_N2 relative to S_N2' displacement. However, other factors may be operative in such a way that the ring can be cleaved via unimolecular ionization to give the delocalized dipolar species (equation 191)



(191)

(route A), or the scission of the cyclopropane bond may be concerted (route B). Path A would lead to racemization at C(5), and path B to retention of configuration at this centre. If the process corresponds to S_N2 displacement, inversion at C(5) would be expected.

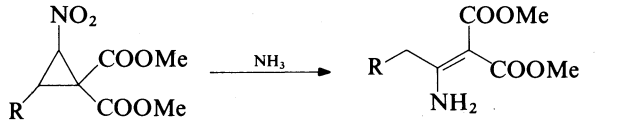
Reaction of the optically active compound **547** with pyrrolidine gives **548**, i.e. it involves inversion at C(5). Consequently, the 1,5-attack corresponds to a traditional nucleophilic displacement (equation 192)[332b].



(192)

(547) **(548)**

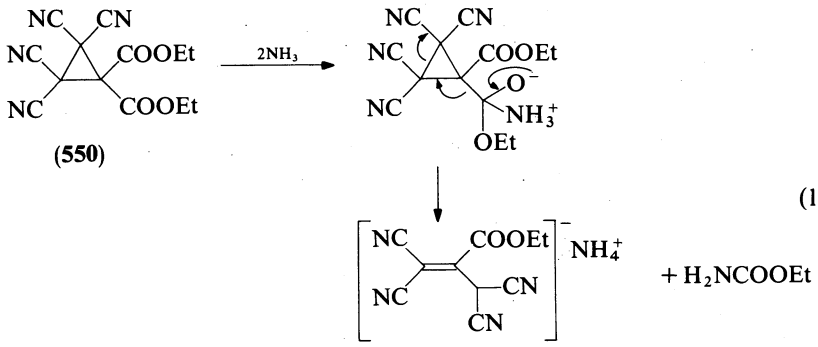
Ammonia is also capable to induce ring cleavage of electrophilic cyclopropanes. Reaction of ammonia with the nitrocyclopropane **417** affords the alkylidenemalonate



(193)

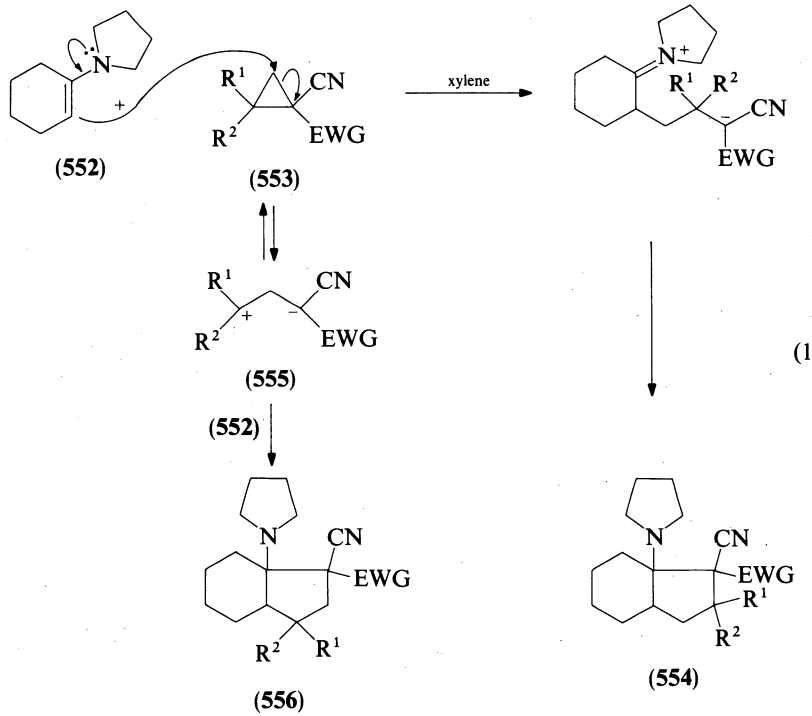
(417) **(549**, 20–79%)

549 (equation 193)[404] Ammonolysis of diethyl 2,2,3,3-tetracyanocyclopropane-1,1-dicarboxylate (**550**) in ether gives rise to **551** (equation 194)[333]. Electrophilic cyclopropanes (**553**) easily undergo cycloadditions with enamines (**552**), providing **554** via a S_N2

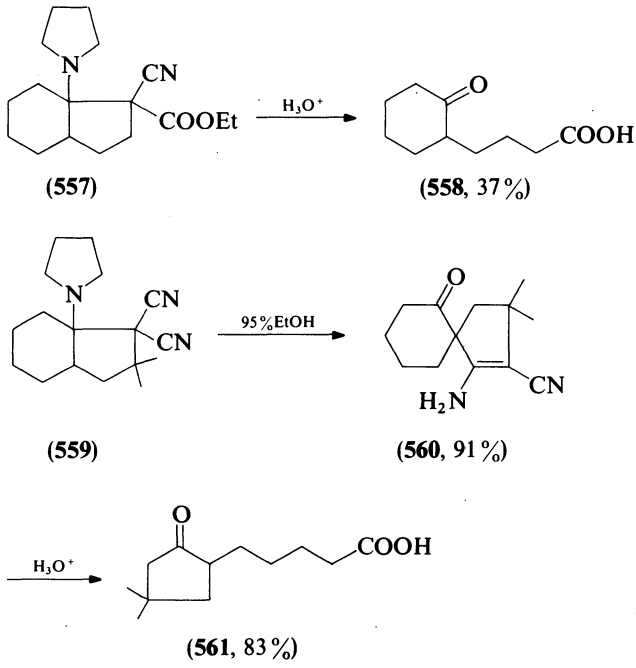


(194)

route (across the 1,3 bond) rather than by way of a zwitterionic intermediate (**555**) (across the 1,2 bond; equation 195)[334, 335]. Acidic hydrolysis of **557** affords 4-(2-ketocyclohexyl)butanoic acid (**558**)[334]. Recrystallization of **559** gives the spiro compound **560** while acid hydrolysis of **559** and **560** provides the keto acid **561** (equation 196)[335]

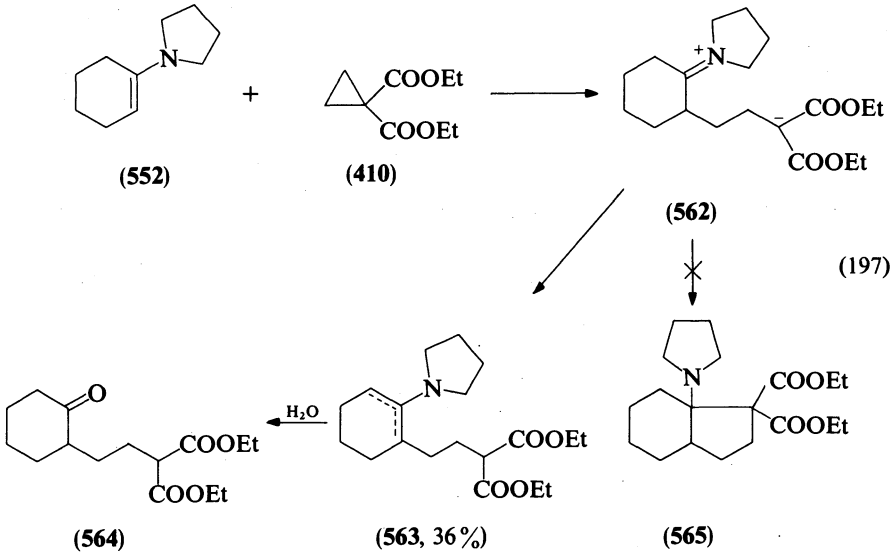


(195)



(196)

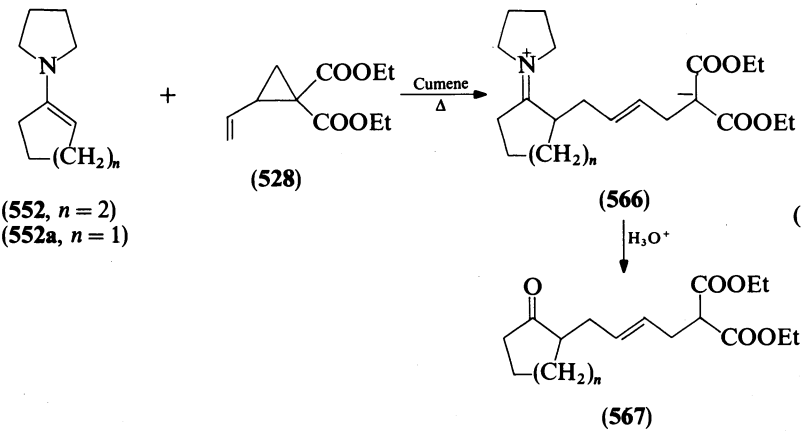
Reaction of the cyclopropane-1,1-dicarboxylate (**410**) with the enamine (**552**) followed by extraction with dilute hydrochloric acid gives rise to the ketodiester (**564**) presumably via the intermediacy of **563** (equation 197)[334]. This difference in reactivity of the diester



(197)

(**410**) and the cyanoester (**553**, EWG = COOR) may be ascribed to several factors. Structure **565** entails a *cis*, highly eclipsed relationship of the ester and the pyrrolidine functions. This source of instability need not be present in **554** if it exists in the *cis*-cyanopyrrolidine relationship. Also the more stringent conditions which are necessary for product formation in the diester case may provoke an equilibrium (Mannich–retro-Mannich) **562** ⇌ **565** which may be irreversibly displaced by the proton transfer **562** ⇌ **563**. In this view, **554** in the cyanoester series, may constitute a kinetic product.

The pyrrolidine enamines of cyclopentanone (**552a**) and cyclohexanone (**552**) undergo exclusive 1,7-addition with the vinylcyclopropane **528** yielding **566**. Mild acidic hydrolysis yields 2-substituted cyclic ketones (**567**) (equation 198)[336].



(**552**, $n = 2$)
(**552a**, $n = 1$)

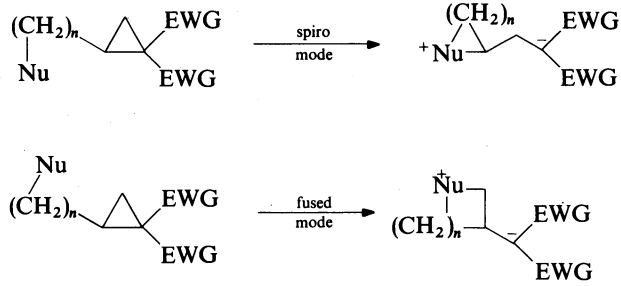
(**528**)

(**566**)

(**567**)

(198)

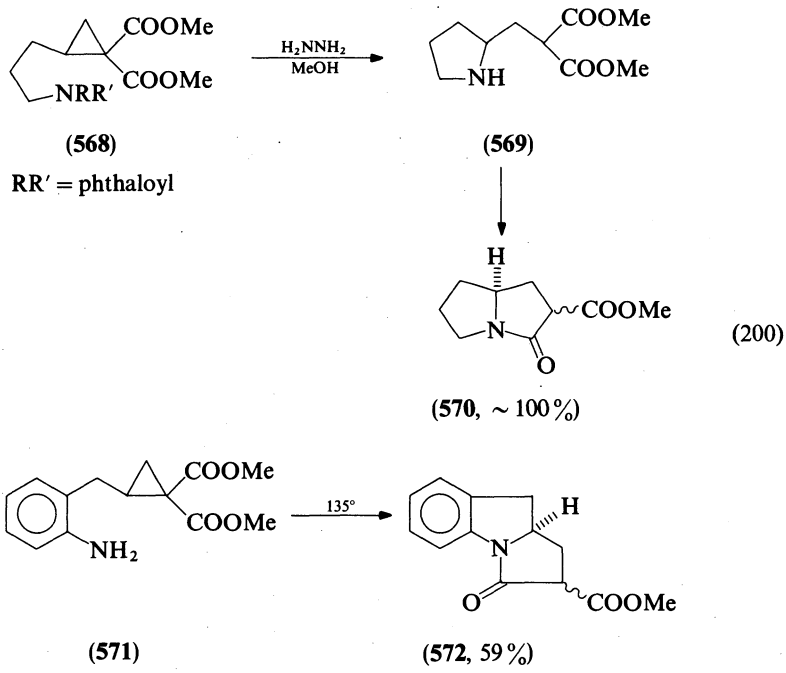
The intramolecular nucleophilic opening of diactivated cyclopropanes by amino functions has been used by Danishefsky to develop new stereospecific routes to *N*-heterocycles. This intramolecular ring-opening can occur in a spiro or in a fused mode (equation 199). It is shown that the spiro mode, leading to five- or six-membered rings,



(199)

predominates over the fused mode, which would produce six- and seven-membered rings, respectively.

The pyrrolizidine system (**570**) is formed when the phthalimidocyclopropane **568** is treated with hydrazine in hot methanol, releasing the amine moiety which undergoes spontaneous ring mutation in the spiro mode leading to **569** and **570** (equation 200)[337,338]. The pyrroloindoline system (**572**) has been prepared in a similar fashion[339].



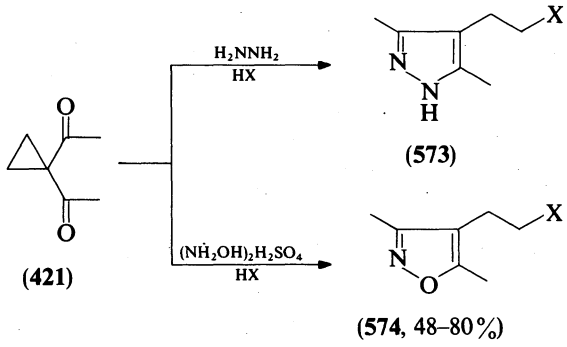
(200)

These intramolecular ring-openings have been utilized in stereospecific syntheses of necine bases[340, 341] and mitosanes[342].

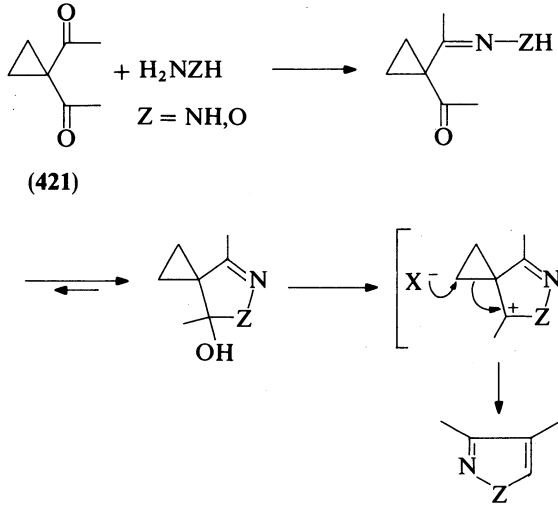
Ring-opening reactions of 1,1-diacetylcyclopropane (**421**) with hydrazine and hydroxylamine derivatives proceed with incorporation of the external nucleophiles (solvent) to afford pyrazoles (**573**) and isoxazoles (**574**) respectively (equation 201)[343, 344]. The probable reaction mechanism is outlined in equation 202.

4. Reaction of electrophilic cyclopropanes with carbon nucleophiles

Ring-opening of electrophilic cyclopropanes by carbanions derived from active methylene functions has already been observed during the synthesis of diethyl

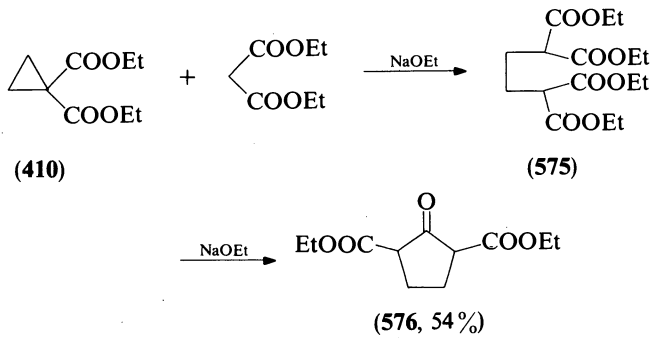


(201)



(202)

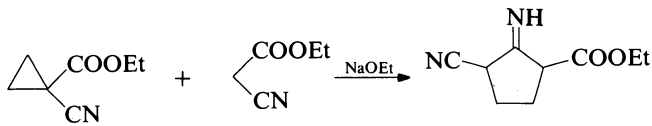
cyclopropane-1,1-dicarboxylate (**410**) from the condensation of 1,2-dibromoethane with diethyl malonate (equation 203). A byproduct, i.e. tetraethyl butane-1,1,4,4-tetracarboxylate (**575**) was formed resulting from a ring-opening by the malonate anion[345, 346]. In the preparation of the tetraester (**575**) from the cyclopropane, partial cyclization of the product occurs to give ethyl 2-oxocyclopentane-1,3-dicarboxylate (**576**) (equation 203)[346]. A similar process is observed in the case of ethyl 1-cyanocyclopropane



(**410**) (**575**) (203)

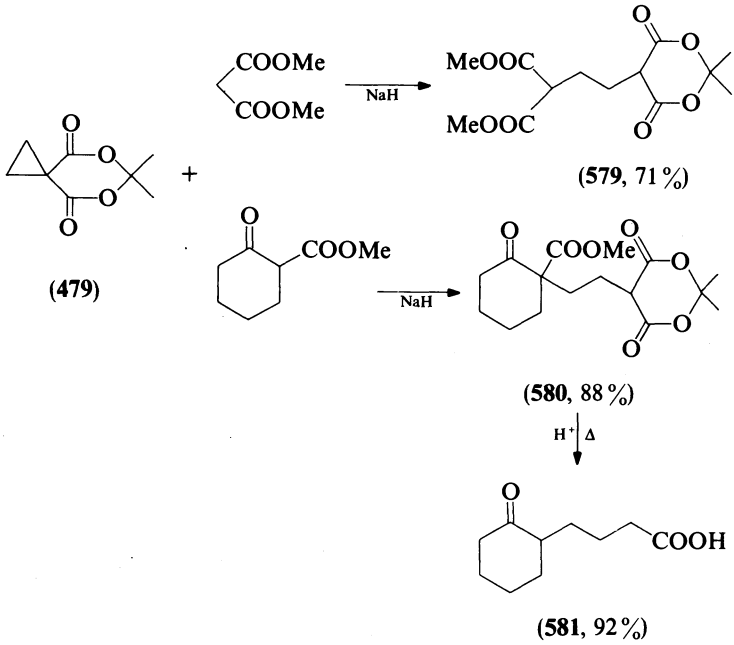
(**576**, 54%)

1-carboxylate (**577**) which forms the imino compound (**578**) (equation 204)[347]. Reaction of the spiro-activated cyclopropane **479** with the sodium salts of active methylene compounds provides ready access to 1,6-dicarbonyl systems such as **579**, **580** and **581** under mild conditions (equation 205)[329].



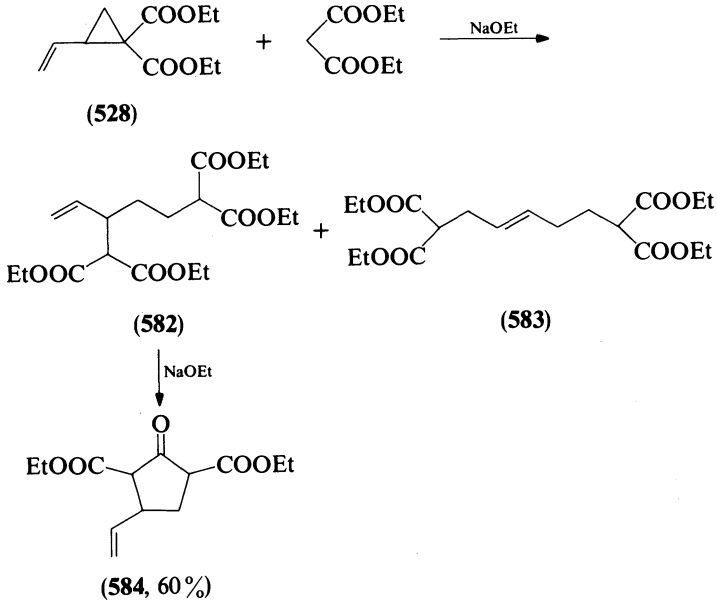
(204)

(**577**) (**578**)



(205)

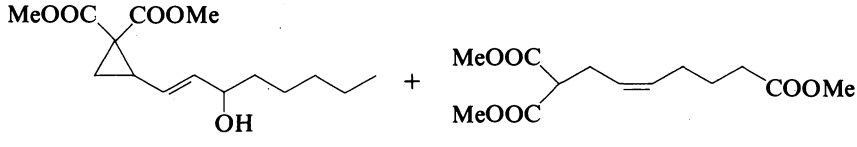
Treatment of ethyl 2-vinylcyclopropane-1,1-dicarboxylate (**528**) with diethyl sodiomalonate gives mainly the tetraester **582** which arises almost exclusively from the 1,5 mode of opening together with minor amounts of the tetraester **583** resulting from a 1,7-opening.



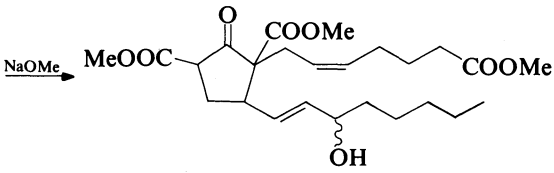
(206)

The former, under the conditions of the reaction, is largely cyclized to diethyl 2-oxo-4-vinylcyclopentane-1,3-dicarboxylate (**584**) (equation 206)[346]. This reaction has been used in the total synthesis of 19-norsteroids for the ring D portion[348].

A similar type of reaction has been used in the preparation of 11-deoxyprostaglandins (**588**) (equation 207)[349,350] and indolechinolizine compounds (**591**) (equation 208)[351,352].

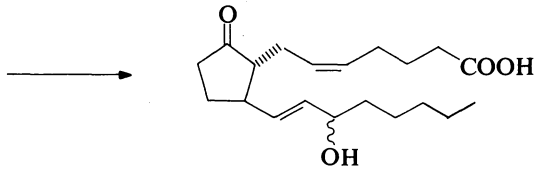


(**585**) (**586**)

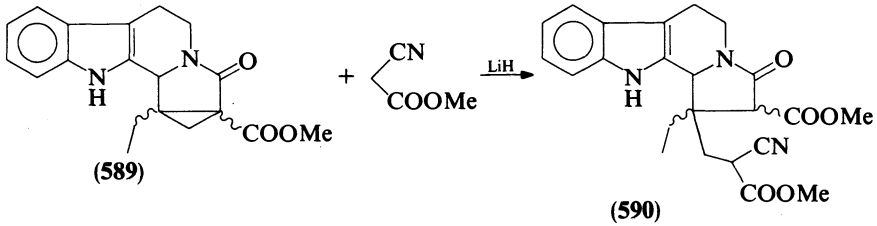


(207)

(**587**, 40%)

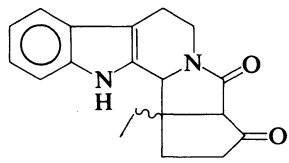


(**588**)



(**589**) (**590**)

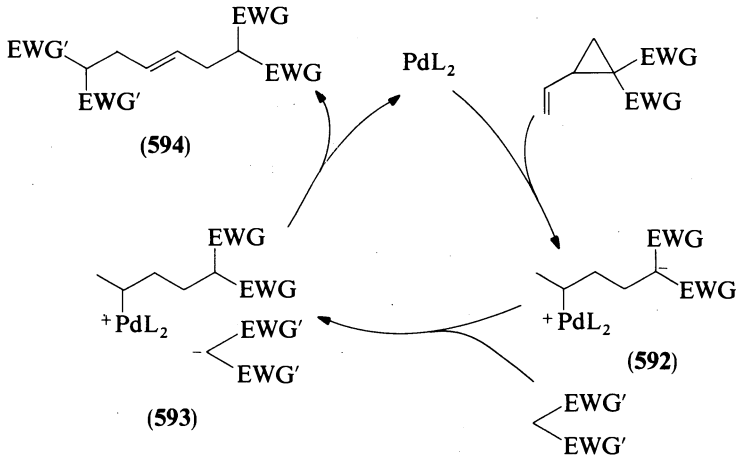
(208)



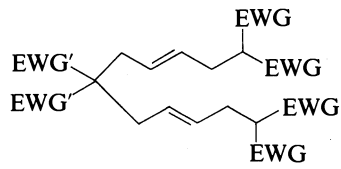
(**591**)

Reaction of the lactam (**589**) with the lithium salt of methyl cyanoacetate gives rise to **590** which can be transformed into the ketolactam (**591**).

Very recently a regiospecific conjugate addition of active methylene compounds to activated vinylcyclopropanes has been achieved under mild and neutral conditions by homogeneous palladium catalysis. It is envisaged that a palladium(0) complex might cleave the 1,2-bond of a cyclopropane to form a zwitterionic intermediate (**592**). This could deprotonate an active methylene compound thus producing a stabilized enolate (**593**) which could add to the π-allyl terminus. By adjusting the cyclopropane : active methylene function ratio, monoalkylation or dialkylation giving rise to **594** and **595** respectively can be achieved (equation 209)[405].



(209)

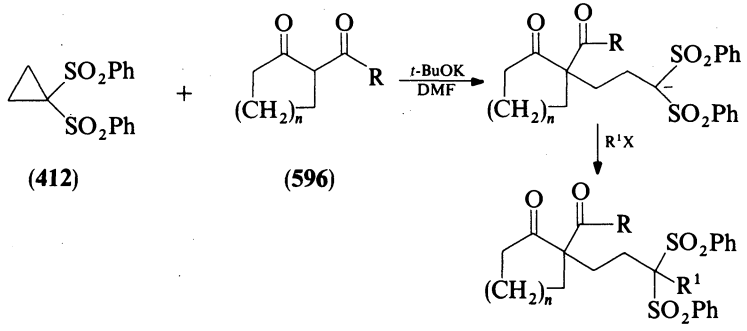


(**595**)

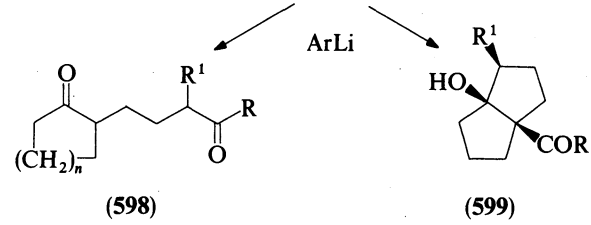
EWG: COOR, SO_2Ph
EWG': COOR, COMe, SO_2Ph
PdL_2: $Pd(PPh_3)_4$

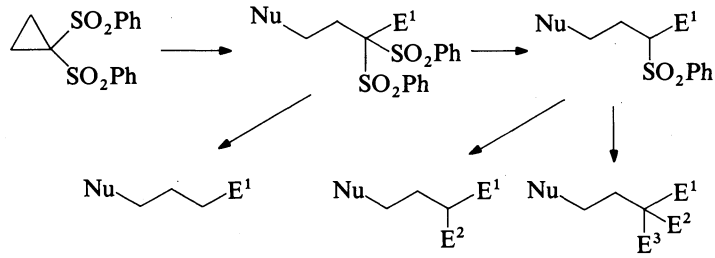
Cyclic β-keto esters and β-diketones (**596**) smoothly effect ring-opening of 1,1-bis(benzenesulphonyl)cyclopropane (**412**) under basic conditions. Reductive cleavage of the resulting sulphones (**597**) by lithium arylides provides routes to **598** and **599** (equation 210)[315]. The bis-benzenesulphonyl compound appears to fulfil the requirements for a propylene 1,3-dipole. The fact that the sulphones can be sequentially removed permits selective introduction of from one to three electrophiles (E) (equation 211). In the case of β-keto esters, such versatility created a novel three carbon insertion between the ester group and the ketone or a cyclopentane annulation[315].

Nitrocyclopropanes also undergo ring cleavage on treatment with sodiomalonate with expulsion of the nitro function providing **600** (equation 212)[404].



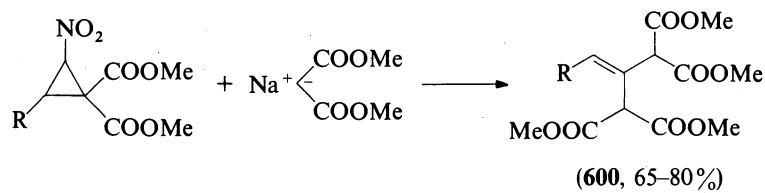
(210)





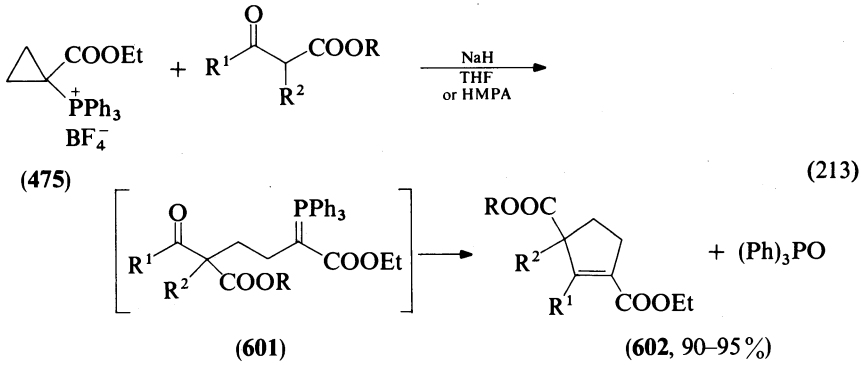
(211)

E^1, E^2, E^3 = electrophiles



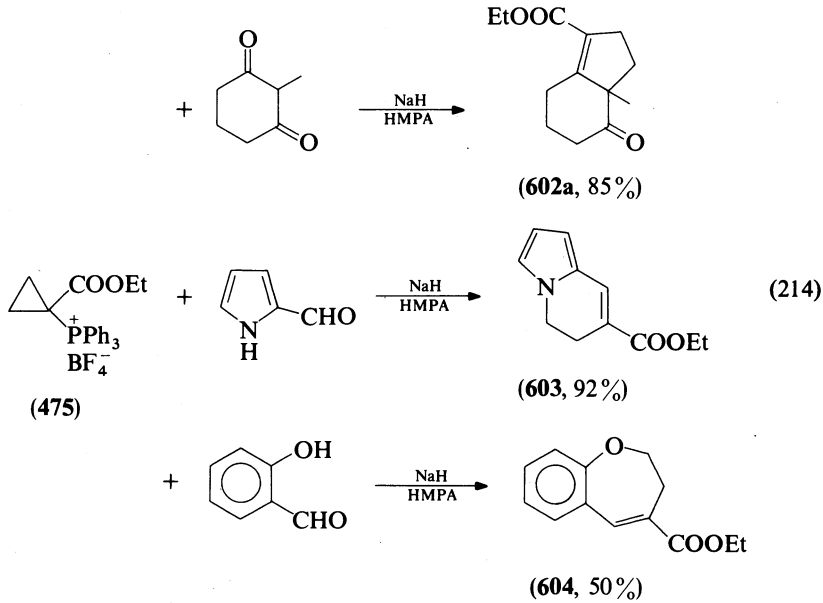
(212)

Carbethoxycyclopropyltriphenylphosphonium fluoroborate (**475**) proves to be an excellent reagent for cycloalkenylation of carbonyl compounds. Reaction of β-keto esters (as their sodium enolates) smoothly produces cyclopentene diesters (**602**) (equation 213)[357]. The mechanism can be most simply viewed as a nucleophilic attack of the enolate on the cyclopropane ring to produce a stabilized ylide, which rapidly cyclizes to the



(213)

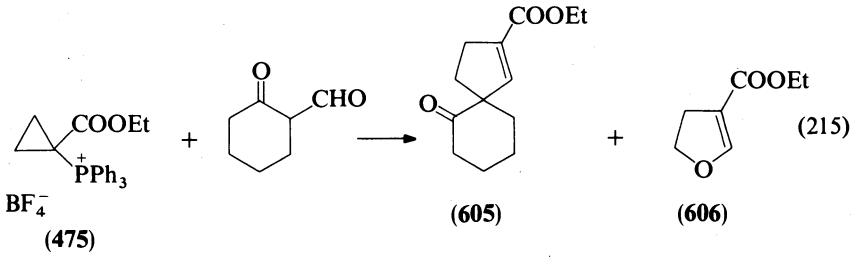
product in an intramolecular Wittig reaction. The three examples in equation 214 further demonstrate the utility of this phosphonium salt as a cycloalkenylation reagent[357].



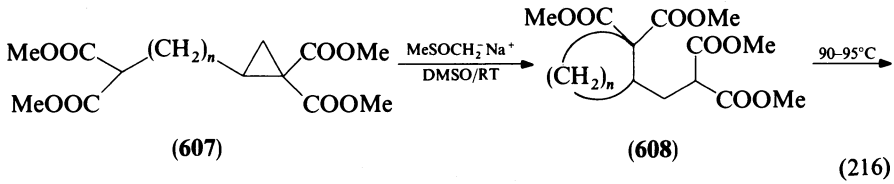
(214)

The reaction between the sodium salt of an α-formylcycloalkanone and the phosphonium cyclopropane has been found to produce spiro compound **605**, together with minor amounts of the dihydrofuran **606** (equation 215). This reaction sequence has been used in the synthesis of spirovetivane sesquiterpenes[353].

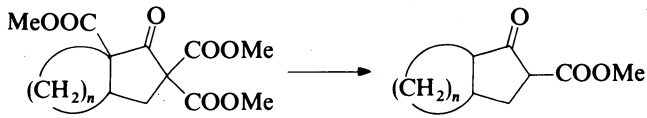
Intramolecular attack of carbanions on electrophilic cyclopropanes has been investigated by Danishefsky[338]. Reactions of the tetraesters **607** with dimsyl sodium–DMSO give rise to an intramolecular homoconjugate addition with a very strong preference for the spiro mode of attack in the ring-opening step. When the reaction is carried out at room temperature compounds **608** are isolated. At 90–95 °C compound **610** is formed through a Dieckmann reaction to **609** and decarbomethoxylation (equation 216)[338]. There is one case where a competition between the spiro and fused mode is



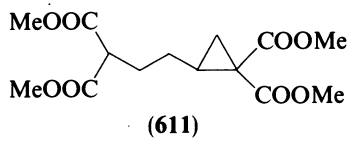
(475) (605) (606) (215)



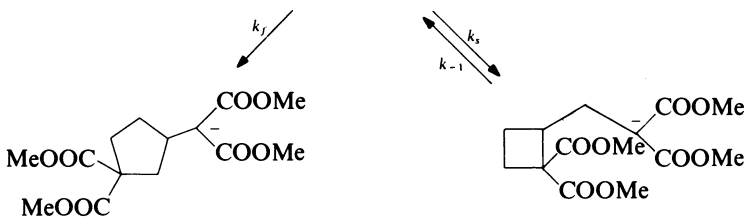
(607) (608) (216)



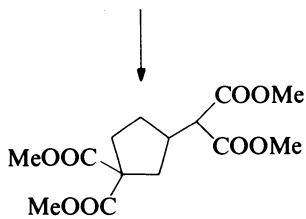
(609) (610, $n = 3$, 77%)



(611)

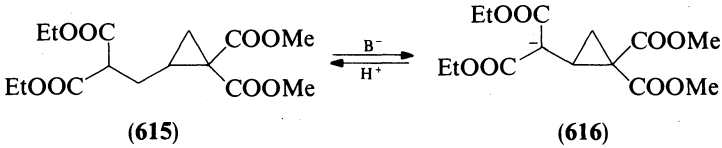


(612) (613) (217)



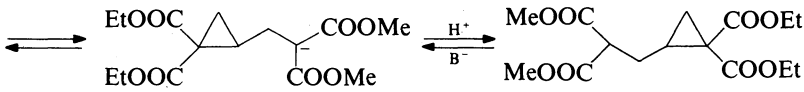
(614, 44%)

observed, where a 2.5:1 kinetic ratio of the anions **613** to **612** is produced. Heating of a solution of **611** in DMSO at 110 °C gives the cyclopentane compound **614** (equation 217)[338]. Treatment of either **615** or **618** with dimsyl sodium affords a 1:1 mixture of the two compounds **615** and **618** but no cyclobutane ring **619** formation is observed (equation 218)[355].

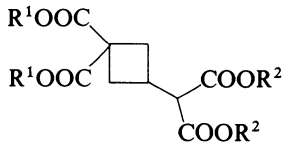


(615) **(616)**

(218)

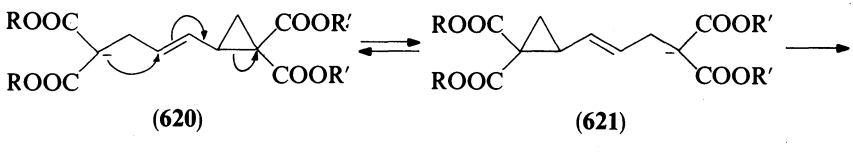


(617) **(618)**

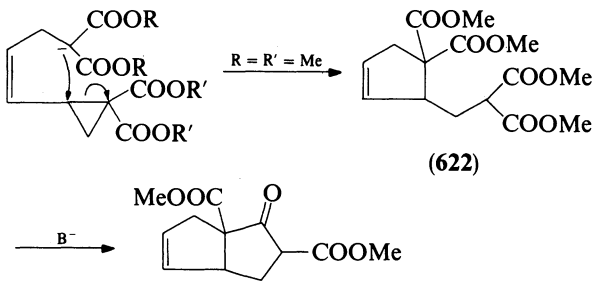


(619)

An interesting case of intramolecular 1,7-attack on a vinyl cyclopropane is observed with carbanion **620**[356]. By using methyl and ethyl esters, intramolecular 1,7-attack occurs essentially instantaneously, since R and R′ are scrambled after a few minutes at room temperature. Intramolecular 1,5-opening gives **622**. At higher temperature Dieckmann condensation takes place providing **623** (equation 219).



(620) **(621)**

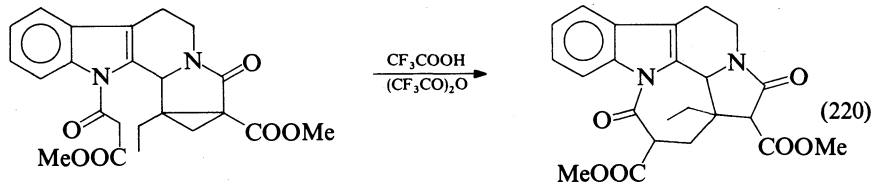


(622)

(219)

(623, 71 %)

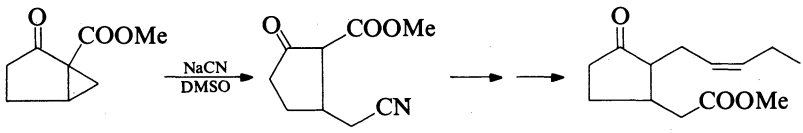
Intramolecular ring-opening of electrophilic cyclopropanes has been used in the synthesis of indolochinolizine compounds (**625**) by treatment of the indole **624** with trifluoroacetic acid/trifluoroacetic anhydride (equation 220)[351,352]. A limited number of



(220)

(**624**) (**625**, 64%)

ring-openings by cyanide ion have been reported[352,358,359]. Reaction of methyl 2-oxobicyclo[3.1.0]hexane-1-carboxylate (**626**) with sodium cyanide in DMSO gives rise to **627** which could be transformed to methyl jasmonate (**628**) in several steps (equation 221)[358].

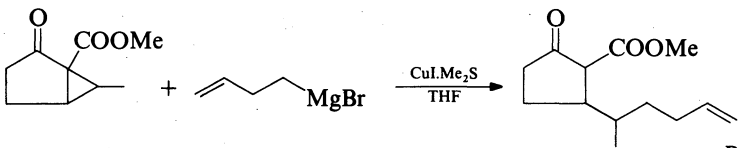


(221)

(**626**) (**627**, 69%) (**628**)

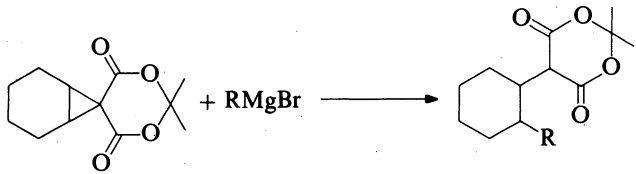
5. Reaction of electrophilic cyclopropanes with organometallic compounds

Homoconjugate addition of Grignard reagents and organocopper compounds to diactivated cyclopropanes has been used in the synthesis of a variety of natural products. Reaction of the bicyclic compounds **629** and **483** with Grignard reagents causes ring cleavage to afford **630** and **631** (equation 222). Ring-opening by organocopper complexes



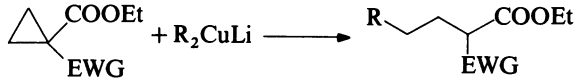
(**629**) (**630**, 60%) Ref. 359

(222)



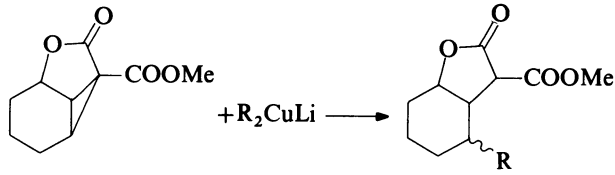
(**483**) (**631**, 80–90%) Ref. 360

(equation 223) has been the subject of several investigations and has found many applications as illustrated by the examples given in equation 224.

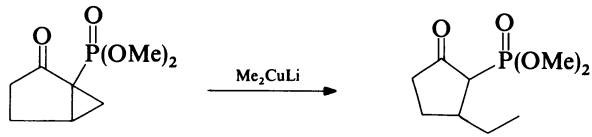


(223)

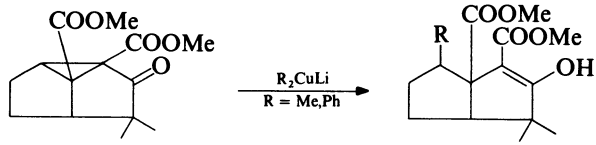
EWG = COOEt: R = Me, *n*-Bu, Ph Ref. 361
EWG = CN: R = Me, vinyl Ref. 362



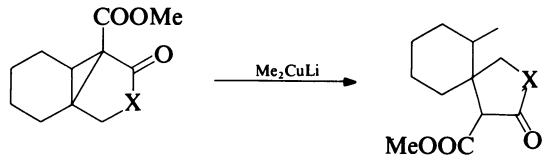
(632) (633) Ref. 362



(634) (635, 90%) Ref. 97

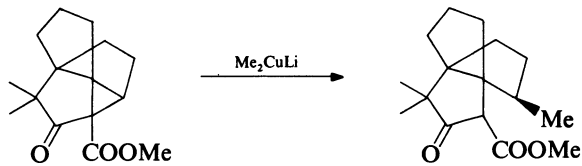


(636) (637, 10–55%) Refs 363, 368

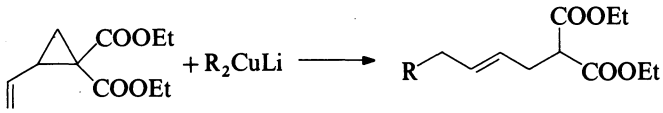


(638) (639, X = O; 90%) Ref. 364

X = CH_2, O

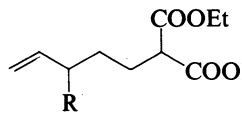


(640) (641, 90%) Ref. 365

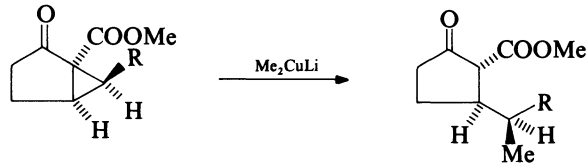


(528) (642, 90%) Refs 306, 361

+

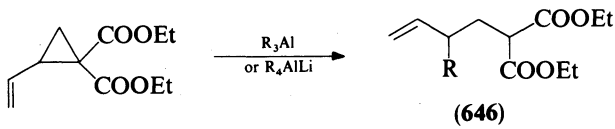


(643, 10%) (224)



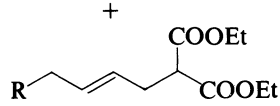
(644) (645) Refs 359, 366

Cuprate-mediated homoconjugate addition to activated cyclopropanes was shown to proceed with inversion of absolute configuration at the chiral carbon of the cyclopropane and the sequence cyclopropanation–homoconjugate addition is therefore one of the few strategies for ring formation that allow direct control of the side-chain stereochemistry[359, 366]. Organoaluminium reagents are able to undergo homoconjugate addition to electrophilic cyclopropanes on condition that a vinyl group substitutes the ring. While trialkylaluminium compounds give rise to a nearly exclusively 1,5-addition product (**646**), the use of tetraalkylaluminium lithium shows a completely different regioselectivity yielding mainly the 1,7-addition product **647** (equation 225)[367]. The same situation is



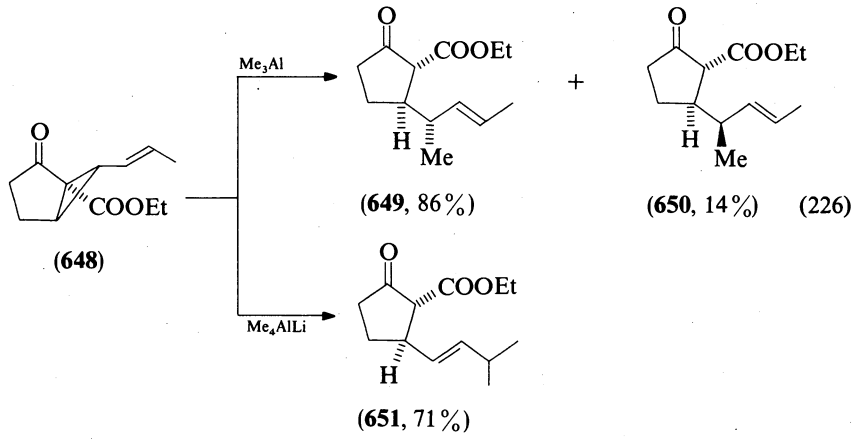
(528) (646) (225)

+

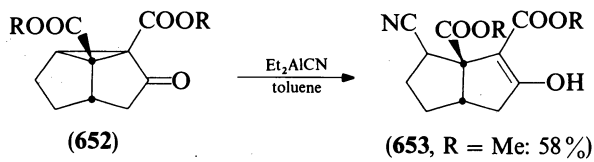


R = Me, Et, C≡C-Ph (647)

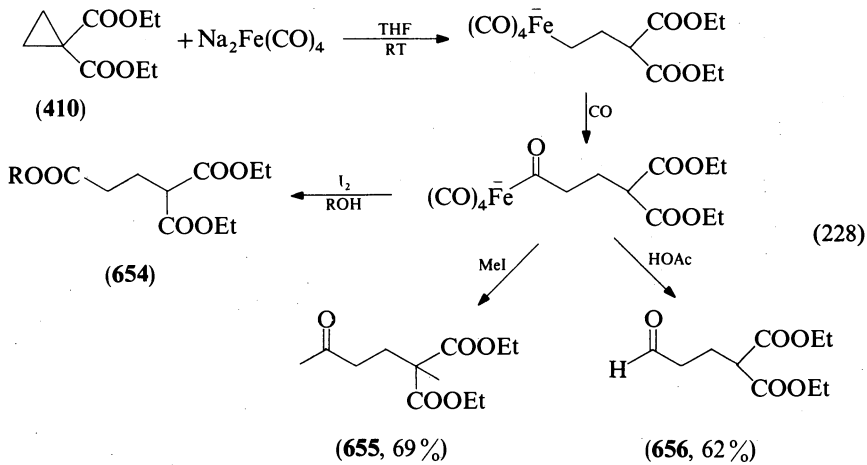
shown in the reaction given in equation 226. Reaction of diethyl aluminium cyanide with tricyclic compound (**652**) allows the introduction of a cyano substituent to provide **653** (equation 227)[363]. A special nucleophilic ring-opening of diethyl cyclopropane-1,1-dicarboxylate (**410**) has been observed on treatment with $Na_2Fe(CO)_4 \cdot 3/2$ dioxane under a CO atmosphere to produce a variety of carbonylated products (**654–656**) (equation 228)[369].



(226)



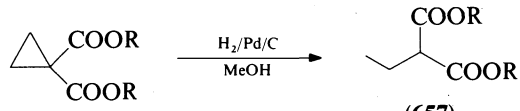
(227)



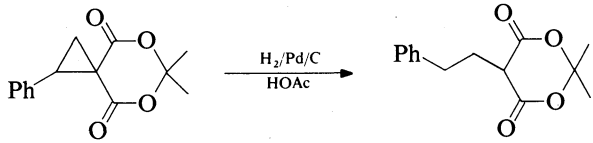
(228)

6. *Reduction of electrophilic cyclopropanes*

Catalytic hydrogenation of electrophilic cyclopropanes normally yields ring-opened products (equation 229)[310, 370]. Catalytic hydrogenation of 1,1-cyclopropanedicarbonitriles (**659**) gives rise to β-cyanoenamines (**661**) via hydrogenation of the dinitriles (**660**) (equation 230)[371, 372]. Hydrogenation of the tetramethyl compound **662** provides **663** via



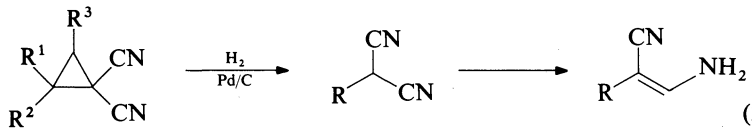
(**657**) Ref. 370



(229)

(**485**) (**658**, 97%) Ref. 310

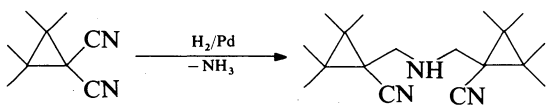
hydrogenation of the imine into an amine followed by addition of the amine across the imine and expulsion of ammonia (equation 231)[372]. Reduction with nucleophilic hydrides



(230)

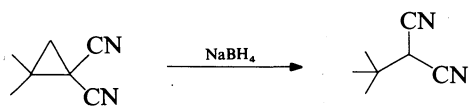
(**659**) (**660**) (**661**)

$R^1 = R^3 = H$; $R^2 = n$-Bu R = 1-methylpentyl
$R^1 = R^2 = Me$; $R^3 = H$ R = *t*-Bu
$R^1 = R^2 = R^3 = Me$ R = *t*-pentyl



(231)

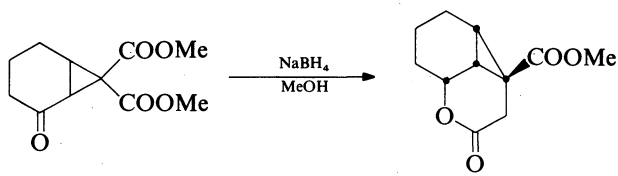
(**662**) (**663**, 83%)



(232)

(**664**) (**665**, 54%)

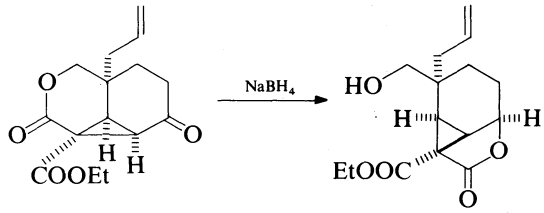
often results in ring cleavage of electrophilic cyclopropanes (equation 232)[183]. However, reduction of the ketodiester **666** with sodium borohydride gives access to lactone **667**



(233)

(**666**) (**667**, 85%)

(equation 233)[373]. In addition, sodium borohydride reduction of **668** has been shown to give the *trans*-esterified product **669** (equation 234)[329].

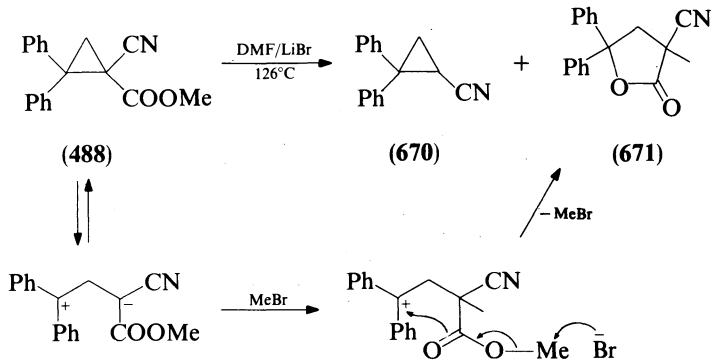


(234)

(668) **(669)**

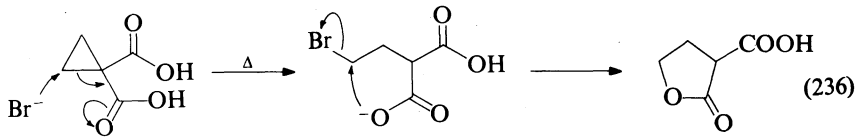
7. Reaction of electrophilic cyclopropanes with halides

In particular cases the reaction of electrophilic cyclopropanes with inorganic halides gives rise to ring cleavage products. In DMF–0.1 M LiBr at 126°C in a sealed tube the cyclopropane **488** affords a mixture of **670** and **671**. The latter product arises from bromide ion attack on the methyl group of the ester to produce methyl bromide and the carboxylate anion which cyclizes, while the former cyclopropane compound **670** results



(235)

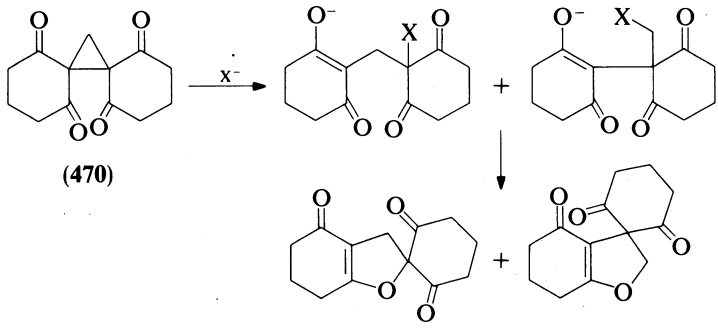
from a similar bromide-induced demethoxycarbonylation (equation 235)[311]. An analogous lactonization is observed when cyclopropane-1,1-dicarboxylic acid (**480**) is heated with potassium bromide (equation 236)[374].



(236)

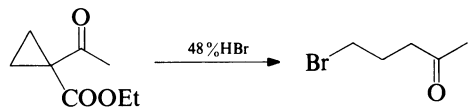
(480) **(482)**

Treatment of the spirocyclopropane **470** with halides results in ring-opening followed by intramolecular ring-closure, yielding mainly **672** together with small amounts of **673** (equation 237)[375].



(470) (672) (673) (237)

Although the reaction of electrophilic cyclopropanes with protonic acids cannot be considered as apparently strictly nucleophilic processes, this reaction can be classified under this section. For example hydrobromination of ethyl 1-acetylcyclopropane carboxylate (**674**) affords 5-bromo-2-pentanone (**675**) (equation 238)[376,377].



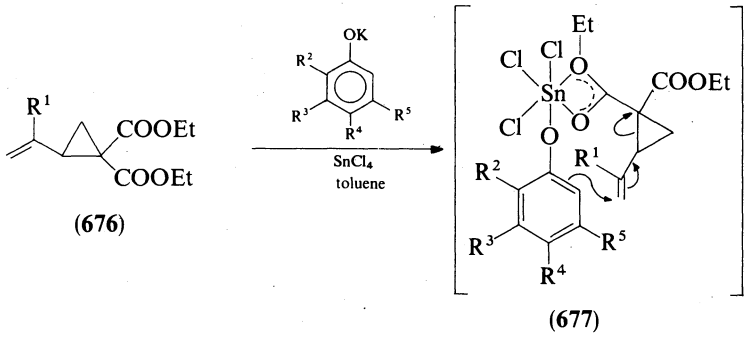
(674) (675) (238)

C. Electrophile-initiated Ring Transformations of Electrophilic Cyclopropanes

While nucleophilic ring-opening of electrophilic cyclopropanes has been the subject of numerous investigations, there are only scant reports dealing with the electrophilic ring-opening of these compounds. It has been shown that diethyl vinylcyclopropane-1,1-dicarboxylates (**676**) are valuable electrophiles in regio- and stereo-controlled alkylation of metal phenolates in the presence of a stoichiometric amount of tin tetrachloride. The products are ethyl 6-(2-hydroxyphenyl)-2-carbethoxy-4-hexenoates (**678**) formed via an *ortho*-specific attack on the phenol ring with exclusive 1,7-homoconjugate addition. The formation of **678** could proceed through the hexacoordinate tin adduct (**677**) in which the vinyl group is placed in a proximity position favourable for an attack by the *ortho* position which also facilitates the attack at the less hindered terminal position of the double bond (equation 239)[378]. It is worthwhile to note that the reaction of ethyl cyclopropane carboxylate with benzene in the presence of aluminium chloride gives 2-methyl-1-indanone via the intermediate ethyl 3-chloro-2-methylpropanoate[379].

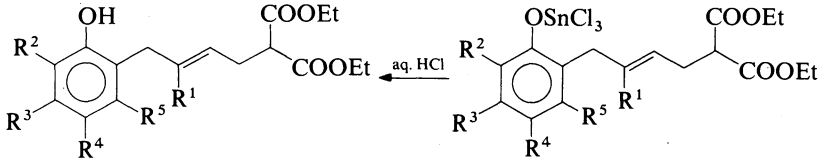
Oxidative decarboxylation of cyclopropane derivative **679** by lead tetraacetate in the presence of copper salts mainly gives tricyclic compounds (**680**) in low yields (equation 240)[380].

Activated cyclopropanecarboxylates **528** and **682** are readily transformed into γ-butyrolactones **681**, **683** and **684** through catalysis by bis(trimethylsilyl)sulphate (BTS) which is characterized by high Lewis acidity and low nucleophilicity. Stereochemically, the reaction takes two pathways. Substrates with a cation-stabilizing group like vinyl give thermodynamically favoured γ-lactones having the thermodynamically more stable arrangement of substituents irrespective of the configuration of the cyclopropane

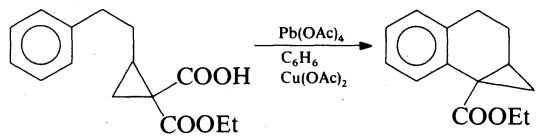


(676) (677)

(239)



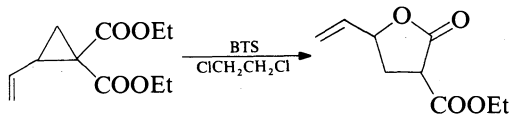
(678, 25–50%)



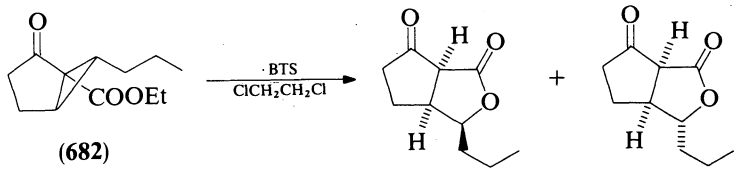
(679) (680, 15%)

(240)

substrates. Compounds without such a cation stabilizing group afford γ-lactones with ca. 70% inversion at the C(2) reaction centre (equation 241)[381, 382]. The BTS catalyst is



(528) (681, 98%)



(682) (683) (684)

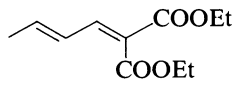
(82:18)

(241)

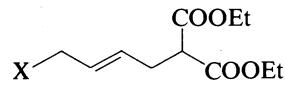
TABLE 3 Reaction products from diethyl 2-vinyl-1,1-cyclopropanedicarboxylate (**528**) with Lewis acid catalysts[382]

Reagent	**681**	**681a**	**681b**
$(Me_3SiO)_2SO_2$	98		
H_2SO_4	61	14	
$Me_3SiOSO_2CF_3$	33	33	
$Me_3SiOClO_3$ (in benzene)	39	—	47 (X = Ph)
Me_3SiI	—	—	87 (X = I)
Et_2AlCl–$AgBF_4$	—	48	31 (X = Cl)

markedly expedient for this transformation as other Lewis acids induced rearrangements to **681a** and/or nucleophilic ring-opening leading to **681b** (Table 3)[382].

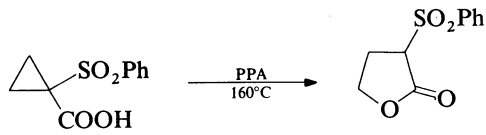


(**681a**)



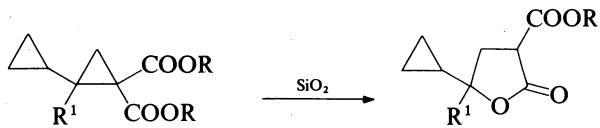
(**681b**)

Transformation of doubly activated cyclopropanes to butyrolactones is performed by treatment with polyphosphoric acid (PPA). For example, the lactonization of 1-phenylsulphonylcyclopropane carboxylic acid (**685**) to **686** proceeds in this way (equation 242)[383]. Transformation of cyclopropane **687** into lactone **688** has been achieved in similar



(242)

(**685**) (**686**, 45%)



(243)

(**687**) (**688**, 45–95%)

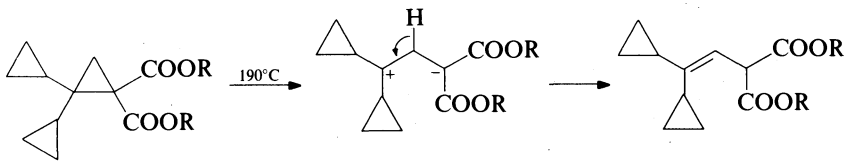
way using silica gel (equation 243)[384]. It was observed that the lactone-forming process is strongly dependent upon the substitution pattern. The presence of two ester functions and at least one additional cyclopropane moiety confers enough vulnerability to the tetra-substituted cyclopropane for the rearrangement to take place.

D. Rearrangements of Electrophilic Cyclopropanes

A limited number of rearrangements of electrophilic cyclopropanes are known in the literature, but synthetic applications have not been encountered except for the vinylcyclopropane (**528**)–cyclopentene rearrangement[385]. This phenomenon is due to the rather

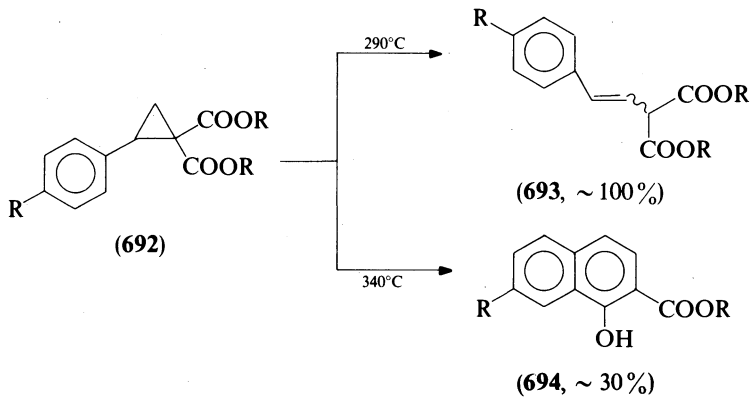
extreme conditions required and/or the particular and specific nature of the cyclopropane derivatives to undergo a rearrangement.

Thermolysis of the 2,2-dicyclopropylcyclopropane **689** at 190°C in the liquid phase gives rise to the β,γ-unsaturated diester **691** (equation 244)[386]. The reaction products

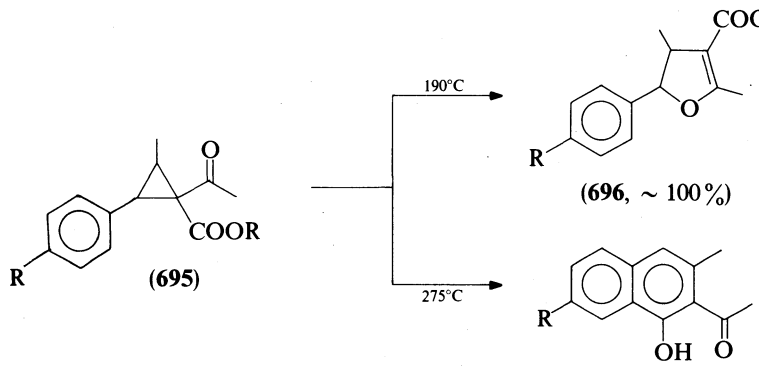


(689) **(690)** **(691)** (244)

formed during the thermolysis of 2-arylcyclopropanes **692** and **695** are strongly dependent upon the temperature range (equation 245). Heating of the diester **692** to 290°C produces



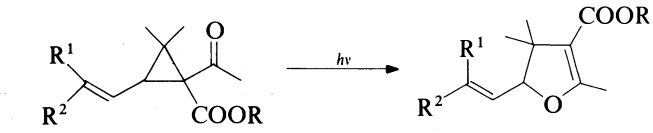
(245)



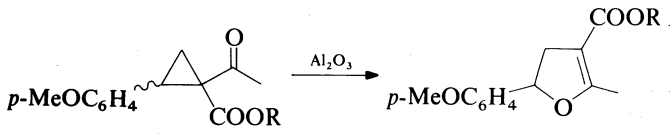
the isomeric olefinic product **693**, whereas raising the temperature to 340°C causes transformation to naphthol derivatives (**694**). On the other hand the acyl derivative **695** upon heating to 190°C produces dihydrofurans (**696**), but at 275°C a naphthol derivative (**697**) is also produced[387]. It is clear that the formation of naphthols must involve fission of

the C–C bond and interaction between the aryl and the carbonyl moieties to form the second six-membered ring.

The rearrangement of acetylcyclopropanes **698**, **700** and **702** into dihydrofurans **699**, **701** and **703** can also be accomplished photochemically[388] or in the presence of aluminium oxide[390] or iodine-sodium iodide (equation 246)[391]. Although the

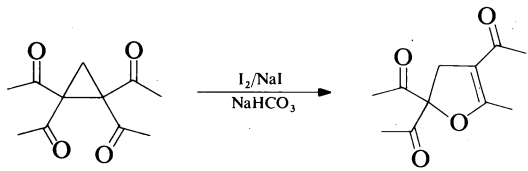


(698) **(699**, 56%)



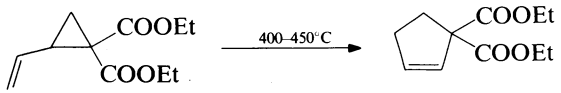
(246)

(700) **(701**, ~ 100%)



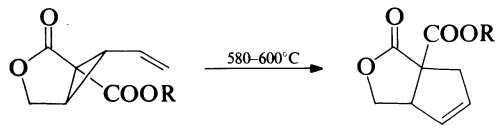
(702) **(703**, ~ 70%)

vinylcyclopropane–cyclopentene rearrangement has attracted mechanistic interest, the synthetic application to electrophilic cyclopropanes has been limited because of the high temperature required (300–500°C)[392]. Pyrolysis of the vinylcyclopropanes **528** and **705** produces the cyclopentene derivatives **704** and **706** in only moderate yields (equation 247)[385, 393]. However, dienylcyclopropane-1,1-dicarboxylates **707** and **709** smoothly



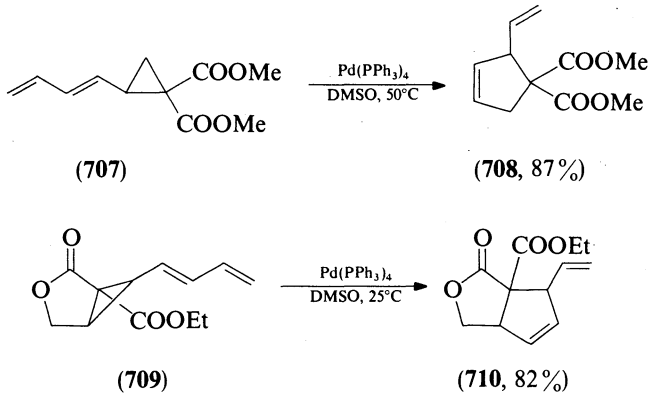
(528) **(704)** Ref. 393

(247)



(705) **(706**, 28%) Ref. 385

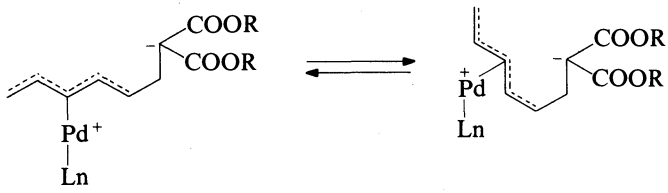
rearrange to five-membered rings **708** and **710** in the presence of a Pd(0) catalyst under mild conditions (equation 248)[394].



(707) (708, 87%) (248)

(709) (710, 82%)

The rearrangement might proceed through nucleophilic attack of Pd(0) on the dienic group to form a zwitterion **711** consisting of π-pentadienylpalladium and stabilized anion moieties under cyclopropane cleavage. The intermediate collapses to form a cyclopentene derivative and the new C–C bond formation exclusively produces a five-membered ring and not a seven-membered one. This regioselectivity is ascribed to the preferred W-type conformation of the pentadienyl group (equation 249).

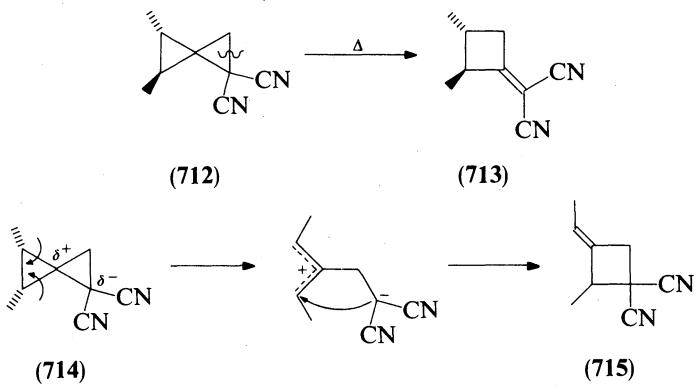


(249)

(711)

Ln = ligand

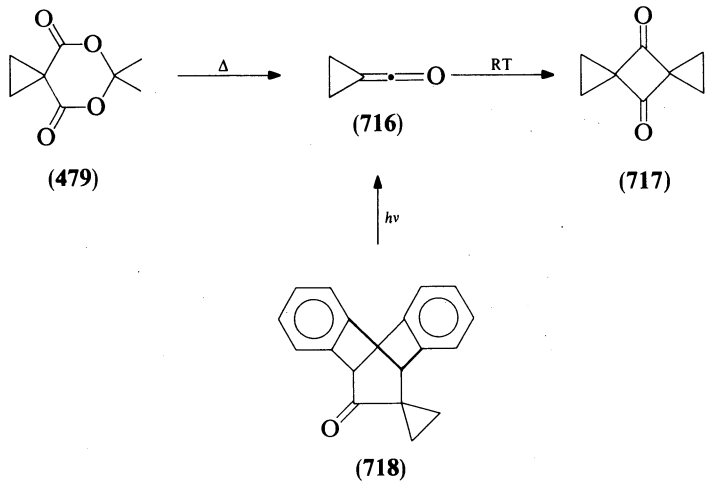
Pyrolysis of the *trans*-dimethyl electrophilic spiropentane **712** at 170°C affords *trans*-2,3-dimethyl 1-(dicyanomethylene)cyclobutane (**713**) whereas the *cis* isomer (**714**) gives rise



(712) (713) (250)

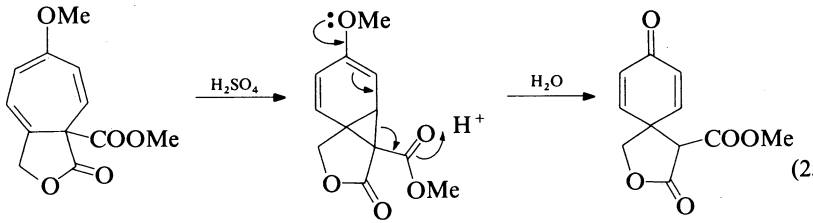
(714) (715)

mainly to an entirely different compound, namely, 2-methyl-3-ethylidenecyclobutane-1,1-dicarbonitrile (**715**) (equation 250)[395]. Pyrolysis of spiroactivated cyclopropane (**479**) at 500°C (0.05 Torr) through a packed silica gel tube readily affords ketene **716**, which on warming to room temperature gives the dimer dispiro-[2,1,2,1]-octane-4,8-dione (**717**) in 45 % yield[406]. The latter compound was also obtained in 40% yield by photolysis of the anthracene–ketene adduct **718** (equation 251)[407].



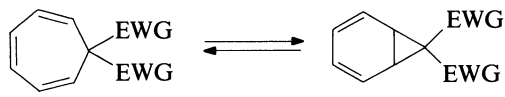
(479) (716) (717) (718) (251)

A particular rearrangement of an intermediate cyclopropane derivative **720** occurs when the methoxycycloheptatriene derivative **719** is transformed into a spiro compound (**721**) on treatment with dilute sulphuric acid (equation 252)[396]. It should be pointed out that the



(719) (720) (721) (252)

valence–isomerism cycloheptatriene (**722**) ⇌ norcaradiene (**723**) is treated in a different chapter (equation 253).



(722) (723) (253)

IV. CONCLUSION

It is the hope of the authors that the compilation of the results gained hitherto in the field of electrophilic cyclopropanes will stimulate further interest in this area. The numerous reactions described in this survey article are an indication of the potential of the title compounds in organic chemistry. Their utility has already been demonstrated in various domains, including natural product synthesis, selective transformations, ring expansions, etc. However, only the basic chemistry of the electrophilic cyclopropanes has been unraveled and results originating from the application of new and modern selective reagents will certainly broaden the scope of its possibilities.

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CHAPTER **10**

Conjugative and substituent properties of the cyclopropyl group

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I. INTRODUCTION

The conjugative and electronic properties of the cyclopropyl group have fascinated chemists for many years, and the results of these investigations have already been summarized in a number of excellent reviews. The current report does not attempt to repeat all the information in these previous summaries, but is intended to provide a general synopsis of the topic at the end of 1984, with an emphasis on the more recent studies.

The review of Charton in 1970[1] entitled *Olefinic Properties of Cyclopropanes* provides very detailed coverage of the understanding as of that date of many of the topics covered in the current review. A very extensive work on cyclopropyl compounds by Wendisch in 1971[2] is particularly concerned with synthesis but also covers many aspects of the substituent effect of cyclopropyl.

More recently Chapter 2 of the monograph by Greenberg and Liebman on strained compounds[3] is devoted to cyclopropane and cyclobutane, with particularly good coverage of the topic of bonding. Similarly the article by de Meijere[4] is devoted to bonding of cyclopropane and the interactions of cyclopropyl as a substituent. A number of specialized articles on cyclopropane chemistry were collected under the title *Perspectives in Small Ring Chemistry*[5] and a 1984 report by Tsuji and Nishida[6a] deals with cycloaddition reactions. Many of the other articles in the current volume are of direct relevance to the topic at hand, and there will invariably be some overlap with these. However, an effort has been made to avoid undue repetition and these chapters should be consulted for background information.

The review consists of five parts, of which the first is a general survey of the substituent properties of cyclopropyl, and the detection and consequences of conjugative interactions of cyclopropyl. The second and third parts involve a more specific discussion of the influence cyclopropyl has on heteroatom and carbon functionalities, respectively. Part

four covers cyclopropylcarbinyl cations, and part five deals with other reactive intermediates.

Some of the abbreviations used include Me, Et, *i*-Pr, *t*-Bu, *c*-Pr, *c*-Pn, *c*-Hx and Ph for methyl, ethyl, 2-propyl, *tert*-butyl, cyclopropyl, cyclopentyl, cyclohexyl and phenyl, respectively.

The literature has been surveyed through 1984 and some selected references through 1985 and early 1986 have also been incorporated during the publication process. The widespread interest in this topic is shown by the continuing appearance of numerous new papers that deserve inclusion in this report, and the need for future summaries is assured.

II. SUBSTITUENT PROPERTIES OF CYCLOPROPYL

A. Methods of Study

The substituent properties of the cyclopropyl group have been assessed by a number of physical methods, including measurements of ionization potentials, ultraviolet spectroscopy, infrared and Raman spectroscopy, nuclear magnetic resonance, mass spectra[6b], dipole moments, and thermochemistry, and the results of these studies up until 1970 were thoroughly covered by Charton[1]. Several of these topics are discussed in detail in separate chapters of this volume, but particular results are cited here when appropriate to illustrate the conjugative powers of cyclopropyl and its use as a probe for reaction mechanisms.

Structure determinations of cyclopropyl derivatives using X-ray crystallography, microwave spectroscopy, electron diffraction, and theoretical calculations has been increasingly emphasized in recent years, and as discussed in later sections the molecular geometries obtained by these methods have been particularly informative as to the substituent interactions of cyclopropyl groups. Molecular mechanics methods have also been applied to structural studies of cyclopropyl derivatives[6c].

Because of its unique structure both the π-conjugative and σ- or inductive electronic properties of cyclopropyl are quite different from alkyl and unstrained cycloalkyl groups. These electronic propoerties are manifested in a variety of ways, including the effect of cyclopropyl on rates and equilibria compared to other substituents, and also in the way that cyclopropyl affects the sensitivity of reactions to other substituents.

B. Cyclopropyl-substituted Acids and Bases

Measurements of the effects of groups on acidity and basicity are a classic method of assessing substituent propoerties, and a variety of these have been measured for cyclopropyl derivatives, as listed in Table 1. There are a number of indications from this table that the electronic properties of cyclopropyl are strongly dependent upon whether or not conjugation with the reaction center is possible. Thus Rhodes and Vargas[7] concluded that the dominant effect of cyclopropyl was π-donation, and that superimposed on this effect there was weak σ-withdrawal, primarily due to high s character in the exocyclic cyclopropyl orbitals. These trends were suggested to be manifested particularly well in the K_A of cyclopropaneacetic acid (**1**) (Table 1), which is modestly more acidic than model compounds. Evidently this acid-strengthening ability is due to the σ-withdrawing effect of cyclopropyl, which operates most strongly on the negatively charged carboxylate anion, but this effect is significantly less than for vinyl, as shown by the comparison to **2**.

The same trend is shown for cyclopropanecarboxylic acid (**3**), which is stronger than aliphatic models, but is significantly weaker than acrylic acid (**4**). The withdrawal in **3** might be masked by π-donation from the ring to the carbonyl group, which would be expected to both stabilize the free acid and destabilize the anion and hence to reduce the

TABLE 1. K_A and K_B values of selected acids and amines

	K_A[a]		K_A[b]	K_A[f]
c-$PrCH_2CO_2H$ (**1**)	1.82×10^{-5}	*m*-*c*-$PrC_6H_4CO_2H$	1.41×10^{-6}	
i-$PrCH_2CO_2H$	1.62×10^{-5}	*p*-*c*-$PrC_6H_4CO_2H$	1.22×10^{-6}	3.00×10^{-5}
CH_2=$CHCH_2CO_2H$ (**2**)	4.32×10^{-5}	*p*-*i*-$PrC_6H_4CO_2H$	1.30×10^{-6}	5.00×10^{-5}
CH_3CO_2H	1.74×10^{-5}	$C_6H_5CO_2H$	2.01×10^{-6}	6.30×10^{-5}
		o-*c*-$PrC_6H_4CO_2H$		7.40×10^{-5}

	K_A[c]	K_A[d]
c-$PrCO_2H$ (**3**)	0.62×10^{-7}	2.33×10^{-5}
c-$HxCO_2H$	0.32×10^{-7}	1.96×10^{-5}
CH_2=$CHCO_2H$ (**4**)	2.96×10^{-7}	8.87×10^{-5}

	K_B[c]		K_B[f]
c-$PrNH_2$ (**5**)	4.6×10^{-6}	*p*-*c*-$PrC_6H_4NH_2$	7.95×10^{-10}
c-$HxNH_2$	68×10^{-6}	*p*-*i*-$PrC_6H_4NH_2$	7.10×10^{-10}
		$C_6H_5NH_2$	3.98×10^{-10}
		o-*c*-$PrC_6H_4NH_2$	1.99×10^{-10}

	K_B[e]		K_A[g]
c-$PrCH_2NH_2$ (**6**)	4.4×10^{-4}	$PhCH_2CO_2H$	2.3×10^{-6}
i-$PrCH_2NH_2$	3.1×10^{-4}	*p*-$MeC_6H_4CH_2CO_2H$	1.8×10^{-6}
		p-*c*-$PrC_6H_4CH_2CO_2H$	1.9×10^{-6}
		p-*c*-(2,2-$Cl_2C_3H_3$)$C_6H_4CH_2CO_2H$	2.5×10^{-6}

[a] H_2O, 25°C, Ref. 7.
[b] 50% H_2O–EtOH, 25°C, Ref. 12.
[c] 50% H_2O–EtOH, 25°C, Ref. 8.
[d] H_2O, 25°C, Ref. 9.
[e] H_2O, 25°C, Ref. 10.
[f] H_2O, 20°C, Ref. 11a.
[g] 50% H_2O–EtOH, Ref. 11b.

acid dissociation. There is good evidence for such conjugation to a carbonyl group, as discussed particularly in Section IV.D.

As a substituent on benzoic acid *m*- and *p*-cyclopropyl are acid weakening (Table 1), indicating a dominant role for π-donation to the ring.

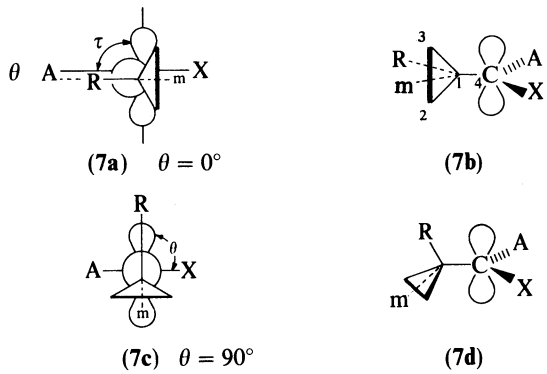
The results with cyclopropyl-substituted amines also reveal the operation of several effects. Cyclopropylamine (**5**) is significantly less basic than cyclohexylamine in solution[8], as expected due to σ-withdrawal from the protonated ammonium ion. However, there is also evidence for significant stabilization of the free amine by *n*-electron donation to cyclopropyl (see Section III.D) so the resultant low basicity is evidently due to a combination of these effects, which operate in the same direction. *p*-Cyclopropylaniline is somewhat more basic than the *p*-isopropyl analog[11], and this effect evidently arises from π-donation to the ring, stabilizing the protonated conjugate acid. The gas phase basicity of **5** is discussed in Section V.I.

There is an old report[10] that cyclopropylmethylamine (**6**) is slightly more basic than isobutylamine, a result that suggests a net electron donation by cyclopropyl. However, as

π-donation would not appear to be feasible in this derivative this interpretation is not altogether satisfactory, and a modern experimental determination of this constant would be desirable.

C. Conformational Dependence of Cyclopropyl Conjugation

The conformational dependence of the π-donor properties of the cyclopropyl group is of decisive importance in the behavior of this substituent, and measurements of ultraviolet spectra, particularly in conformationally fixed derivatives, have been especially useful in elucidating this effect[13–18]. Maximum conjugation occurs when the plane of the cyclopropyl ring is most nearly parallel to the adjacent π-system, and this is most commonly expressed as an angular dependence, with overlap at a maximum in the bisected conformation **7a**, **b** and at a minimum in the perpendicular arrangement **7c**, **d** (Figure 1).



(7a) $\theta = 0°$ (7b)

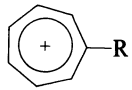
(7c) $\theta = 90°$ (7d)

FIGURE 1. Geometries of the cyclopropane ring and an adjacent p orbital in bisected (**7a,7b**) and perpendicular (**7c,7d**) conformations (m is the midpoint of the C(2)–C(3) bond)

Because the cyclopropane ring may have unequal bond lengths and may also be tilted relative to the adjacent π-system, which itself may be distorted from a trigonal planar geometry adjacent to the ring, some care is necessary in defining the angle between the systems. Thus based on the definitions presented by Van-Catledge and coworkers[17] the angle θ can be defined as the angle between the planes defined by R–C(1)–C(4) and C(1)–C(4)–X (Figure 1). The angle τ is defined as the angle between cyclopropyl plane and the plane defined by C(1)–C(4)–X and will equal $90° - \theta$ unless the cyclopropyl plane is twisted. The angle ϕ is defined as the angle between the cyclopropyl plane and that defined by *m*–C(1)–C(4) where *m* is the midpoint of the C(2)–C(3) bond. Thus ϕ is also $90°-\theta$ for the symmetrical case. Van-Catledge and coworkers[17] concluded that although these two deviations would affect the conjugation of the cyclopropyl with the adjacent π-system, nevertheless the angle θ was of primary importance, at least for determining λ_{max} of cyclopropyl ketones.

The circular dichroism spectra of vinylcyclopropanes have been used to assign the absolute configurations of these compounds[18].

The UV spectra of cyclopropyltropylium ions have been suggested as an alternative probe for elucidating the interaction of cyclopropyl with an adjacent π-system because of the large shifts involved[19]. As shown for **8** and **9** there is a very large shift to longer wavelength absorption for cyclopropyl relative to isopropyl-substituted tropylium ion[19].



(8) (R = *c*-Pr) λ_{max} 247 nm (ε 29 800), 327 nm (ε 12 300)

(9) (R = *i*-Pr) λ_{max} 225 nm (ε 32 200), 274 nm (ε 14 400)

In another study of cyclopropyltropylium ion the rate of Cr(II) reduction of **8** to the radical has been measured, and it was found that methyl substituents on the ring positions adjacent to the cyclopropyl evidently twisted the *c*-Pr ring out of conjugation, as manifested in a faster than anticipated rate of reduction[20].

D. X-Ray Structure Determination of Cyclopropyl Compounds

A comprehensive analysis of the available X-ray structural data of cyclopropane derivatives has been carried out by Allen[21,22] and shows systematic geometrical changes that are evidence for conjugation with π-acceptor groups. In particular there was a shortening of the C(2)–C(3) distal bond by an average amount δ (relative to the mean ring C–C distance for that compound) characteristic of each substituent and a concomitant lengthening of the C(1)–C(2) and C(1)–(3) vicinal bonds by approximately δ/2 (Table 2). Furthermore, examination of the effect of conformation on these bond length changes suggested that only bisected geometries gave these characteristic changes, and that when there were deviations of more than 30° from this arrangement conjugation became ineffective and the geometrical deformations became negligible.

TABLE 2. X-Ray structural parameters for cyclopropyl derivatives with substituents X

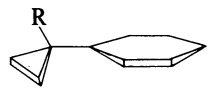
X	C=O	C=C	Ph	N=C	C≡N	N=N
δ(Å)[a]	−0.026	−0.022	−0.018	−0.018	−0.017	−0.014

[a] Average change in C(2)–C(3) relative to mean ring C–C distance for each derivative.

In the case of multiply-substituted cyclopropane rings the effects of the substituents appeared to be additive. This observation indicates that the cyclopropyl ring does not transmit conjugative effects between the substituents (see Section II.1)[22a].

The exocyclic bond distances to the attached groups were also examined[22b], and included saturated substituents not expected to be π-acceptors, conjugated π-acceptors, and π-acceptors twisted out of the range of effective conjugation. In this way both the hybridization and conjugative effects on the bond distances could be identified. As a result of this analysis the effective hybridization of cyclopropane was calculated as $sp^{2.25}$ (30.8 % s character) in the exocyclic bonds and $sp^{4.20}$ (19.2 % s) in the ring bonds[21]. A comparison of the conjugating abilities indicated that cyclopropyl was 71 % as effective as vinyl in interactions with alkenyl and carbonyl groups[22b].

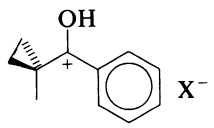
In phenylcyclopropanes the perpendicular conformation **10** is favored in the majority of the cases observed[22a]. It was suggested[22a] that this preference probably arose from steric factors but was assisted by π-donation from phenyl to the 4e′ LUMO orbital of cyclopropyl, which has a large coefficient at C(1). This interpretation is in interesting



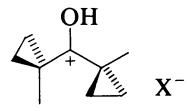
(10)

contrast to the view that π-donation occurs in a preferred bisected conformation from cyclopropyl to phenyl, at least in the excited states studied by UV spectroscopy[13–15] (see also Section IV.C).

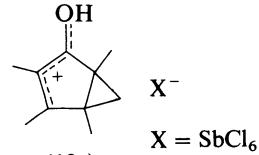
Molecular structures of the cyclopropylcarbinyl cation salts **10a–c** have been determined by X-ray[23a,b]. Both **10a** and **10b** show a bisected geometry that optimizes cyclopropyl conjugation with the cationic center, whereas in **10c** such conjugation could lead to antiaromatic destabilization, and it was suggested that the structure reflected geometrical distortion to avoid interaction of the cyclopropyl group with the allyl cation portion of **10c**.



(10a)



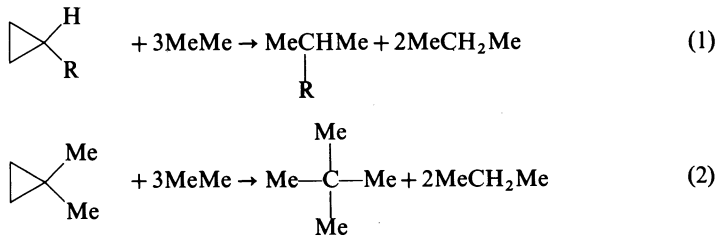
(10b)



(10c)

E. Thermochemical Measurements

It has recently been argued[24] that the existing body of thermochemical data is inadequate to demonstrate quantitatively the effects of cyclopropyl conjugation that has been claimed for many systems. New measurements of the heats of vaporization of cyclopropyl cyanide and cyclopropylbenzene were made, and using these data and others in the literature the stabilities of a series of substituted cyclopropanes were compared to the corresponding 2-substituted propanes by the isodesmic reactions 1 and 2 shown in Scheme 1[24].



R	H	CN	Me[b]	NH_2	Ph
$\Delta H°$[a] (kcal mol^{-1})	−27.4	−27.5	−27.8	−28.2	−24.8

[a] Reaction 1 unless noted. [b] Reaction 2.

SCHEME 1

The heats of reaction for R = H, CN, CH_3, and NH_2 are essentially identical, and this result indicates that there is no significant thermochemical stabilization that results from any of these substituents on the cyclopropyl ring. In the case of phenylcyclopropane the heat of reaction was less exothermic by 2.94 kcal mol^{-1} than the mean of the other four values, and of this 1.05 kcal mol^{-1} was ascribed to steric hindrance in isopropylbenzene, leaving 1.89 kcal mol^{-1} attributed to stabilization due to conjugation in cyclopropylbenzene[24].

It was suggested that the failure to detect stabilization due to conjugative interactions in substituted cyclopropanes may arise from other destabilizing interactions such as unfavorable electronic interactions or steric effects[24]. Thus even though conjugation could favor certain structures, other unfavorable interactions in cyclopropanes substituted with electronegative groups could result in a situation where there was no net stabilization.

Other thermochemical studies of conjugative interactions of cyclopropanes have involved equilibration of conjugated and non-conjugated isomers, as in **11**[25] and **12**[26]. A

(11a) **(11b)** **(12a)** **(12b)**

stabilization of 1.2 kcal mol^{-1} was suggested for conjugation of the double bond in the first case[25], and the conjugated isomer made up of 80% of the equilibrium mixture in the second[4,26]. Thermochemical data on cyclopropyl cations are considered in Section V.I.

F. Substituent Parameters

The effect of cyclopropyl on reactivity and molecular properties can be conveniently expressed as substituent parameters, as summarized in Table 3[7,11,12,25-45]. The unique properties of cyclopropyl require, however, that these parameters should not be applied uncritically, because cyclopropyl may respond in an unusual way to the particular probe used to define the parameters for 'normal' substituents. These special properties of cyclopropyl include its ability to act as a π-donor not only to charged systems but to other π-acceptors as well, its ability to serve as a π-acceptor with donors such as NH_2 and OH (see Sections III.D and III.E), the conformational dependence of the preceding two effects, and the σ-withdrawing influence of the group.

TABLE 3. Cyclopropyl substituent constants

σ_m	-0.07^a, -0.102^b, -0.14^c	
σ_p	-0.19^e, -0.21^a, -0.22^d, -0.23^c, -0.24^e	
σ_m^+	-0.041^f, -0.03^g, -0.036^d	
σ_p^+	-0.410^h, -0.439^i, 0.45^d, $-0.46^{j,t}$, -0.473^k, -0.481^m, -0.54^n	
σ_R°	-0.13^v	
σ_R^+	-0.27^l, -0.38^o, -0.35^d	
σ^*	$+0.11^p$, -0.14^q, -0.08^q, -0.15^w	
$\sigma_{CH_2X^*}$	0.011^r	
σ°	-0.21^s, -0.10^d	
σ_I	0.01^t, -0.08^v	
σ^{C^+}	-1.33^u	
σ_p^+ (perp)	-0.21^x	$\sigma_0^+ = -0.365^k$

[a] Ref. 27. [b] Ref. 28. [c] T. F. Corbin, PhD dissertation, quoted in Ref. 7. [d] Ref. 11b. [e] Ref. 29. [f] Ref. 12. [g] Ref. 30. [h] Ref. 31. [i] Ref. 32. [j] Ref. 33. [k] Ref. 35. [l] Ref. 45. [m] Ref. 34. [n] Ref. 43. [o] Ref. 36. [p] Ref. 37. [q] Ref. 38. [r] Ref. 7. [s] Ref. 40. [t] Ref. 42. [u] Calculated from data in Ref. 48. [v] Ref. 41. [w] Ref. 39. [x] For a perpendicular conformation, see Ref. 42.

The substituent parameters σ_m and σ_p are derived from benzoic acid ionization, and the $\sigma_{CH_2X^*}$ values follow from the acidity of **1** (Table 1), and the factors that influence these quantities have already been discussed in Section II.B.

The first three σ^* values listed are derived from IR correlations[37, 38] and the last from polarography[39], and these methods clearly give widely divergent answers. The σ°[40] and σ_R°[41] values are derived from ^{19}F-chemical shift measurements which are available for a large number of structural types.

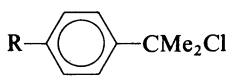
The rates of solvolysis of substituted cumyl chlorides (equation 3) are used to define σ_m^+ and σ_p^+ parameters, and this reaction has been studied in several different laboratories[12, 31, 33, 34]. These constants reflect the enhanced stabilization when direct conjugation of the *p*-substituent with the cationic center is possible and clearly demonstrate the importance of this effect for cyclopropyl.

(3)

(13)

Several other processes found to correlate with σ^+ parameters have been used to derive secondary values for cyclopropyl, and these are in general agreement with those from solvolysis[30, 35, 43].

The conformational dependence of cyclopropyl conjugation was illustrated in solvolysis of methyl-substituted cyclopropylcumyl chlorides[33]. Thus for solvolysis of 2-aryl-2-propyl chlorides (**14**) there was an acceleration by a factor of 154 for replacement of the *p*-H by cyclopropyl, whereas for the 2-(3′,5′-dimethylphenyl)-2-propyl chloride (**15**) the acceleration was decreased to a factor of 9.0[33].



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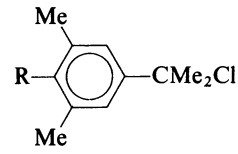
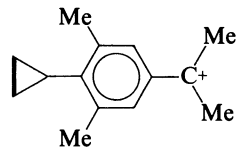


(15)

k(*c*-Pr)/k(H)	154	9.0

The decreased acceleration due to the cyclopropyl group was attributed to the requirement that the cyclopropyl was forced by the two adjacent methyl groups to assume the perpendicular conformation **16** which prevented optimum conjugation[33]. The inductive effect of cyclopropyl in this conformation is an item of some interest, and is considered further in Section V.D.



(16)

The effective size of the cyclopropyl group is a matter of considerable importance. However, the quantitative measurement of the size of this group gave a very deceptive

answer[44]. The upsilon (υ) parameter has been derived from geometrical calculations, and found to correlate with rates of acid-catalyzed esterification[45,46]. However the υ value derived from reactivity for cyclopropyl did not appear to be a realistic measure of size when compared to other alkyl groups: *c*-Pr (1.06), Me (0.52), Et (0.56), *i*-Pr (0.76), and *t*-Bu (1.24), and as noted[44] this result indicated that a resonance component was contributing to the value. The effective size of cyclopropyl will depend on the conformation.

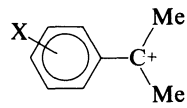
The σ^{C^+} constants for substituents are derived from the chemical shift δ^{C^+} from Me_4Si of the formally positively charged carbon in long-lived substituted cumyl cations (**13**) (Table 4)[47,48]. As can be seen from the data the position of cyclopropyl is unique in this

TABLE 4. δ^{C^+} and σ^{C^+} parameters for alkyl groups

p-R	H	Me	Et	*i*-Pr	*t*-Bu	*c*-Pr	*c*-Bu	*c*-Pn	*c*-Hx
δ^{C^+}	255.7	243.6	243.7	244.0	244.5	231.6	241.6	241.6	242.6
σ^{C^+}[a]	0	−0.67	−0.67	−0.65	−0.62	−1.33	−0.78	−0.78	−0.73

[a] Calculated from δ^{C^+} by the procedure of Ref. 47.

series, with an upfield shift of 10.0–12.9 ppm from the other alkyl groups, which differ from one another by only 2.9 ppm. Although ^{13}C-chemical shifts cannot be directly correlated with charge densities or ion stabilities these data nevertheless indicate a strong π-donor ability by cyclopropyl.



(13)

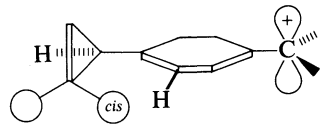
A number of σ_p^+ values for substituted cyclopropyl groups have also been derived from solvolysis reactions[34], as shown in Table 5, along with one value from aromatic detritiation[35].

TABLE 5. σ_p^+ Values of substituted cyclopropyl groups[a]

trans-2-Cl	*cis*-2-Cl	*trans*-2-Br	*cis*-2-Br	2,2-Cl_2	2,2-Br_2	1-Me[b]
−0.247	−0.226	−0.276	−0.200	−0.043[c]	−0.038	−0.525

[a] Ref. 34 unless noted.
[b] Ref. 35.
[c] Ref. 11b reports −0.036.

The electronegative halogens all reduce the electron-donating ability of the cyclopropyl group, with an average reduction in the magnitude of σ_p^+ by 0.24 for one halogen and 0.44 for two. Similarly the electron-donating ability of the 1-methyl group increases the magnitude of σ_p^+. The greater magnitude of σ_p^+ for the *trans*-relative to the *cis*-2-halo compounds is further support that a bisected conformation is favored in these solvolysis transition states, for as shown in **13a** a *trans*-2-substituent on a bisected cyclopropyl ring is unencumbered, whereas a *cis*-2-substituent suffers from steric interactions with an adjacent hydrogen. The value for the 1-methylcyclopropyl substituent probably is diminished by steric interactions of the methyl with the ring, as discussed in Section IV.C.



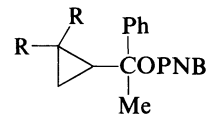
(13a)

An essentially additive effect of ring substituents on the π-donor ability of cyclopropyl in generation of carbocation derivatives was also shown in the solvolysis of a series of methyl-substituted cyclopropylcarbinyl dinitrobenzoates (ODNB) (equation 4) studied by

(4)

Schleyer and van Dine[49]. These authors reported rates for three monomethyl derivatives and six dimethyl derivatives, and found that the rate accelerations per methyl group were all in the range of 5–11. It was argued that these results were all consistent with electron donation by bisected cyclopropyl groups[49].

It was observed that the rate of solvolysis of the 2,2-dimethyl derivative **17a** was accelerated by a factor of 12 relative to the unsubstituted derivative **17b** in 90% acetone at 25 °C, whereas the 2,2-dichloro analog **17c** was 1.4×10^4 times less reactive than **17b**[50]. These rate effects are consistent with the σ_p^+ constants for such substituted cyclopropyl groups discussed above.



R = Me **(17a)**, H **(17b)**, Cl **(17c)**

(OPNB = *p*-nitrobenzoate)

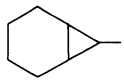
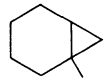
The rate acceleration for the 2,2-dimethyl derivative in the reaction of equation 4 was a factor of 92 relative to the unsubstituted derivative[49]. The smaller ratio for **17a** may be partly due to an attenuation of the substituent effect in the more stabilized carbocation from **17a**, and also to steric interactions in the ion from **17a** which interfere with the preferred geometry for conjugation by both the aryl and cyclopropyl groups.

G. Charge Transfer and Ionization Potentials

Electronic excitation of cyclopropyl derivatives is discussed in detail in other chapters of this volume but because of the importance of some of these studies for the elucidation of the conjugative abilities of this group some mention of this topic here is warranted.

Traylor and coworkers carried out extensive studies of the charge transfer spectra of substituted aryl derivatives with TCNE, including those with cyclopropyl substituents[51–53]. It was found that there was a general correlation of these charge transfer frequencies with the electron donor abilities of the substituents, as measured by solvolytic reactivities or by σ_p^+ constants. Some of the data are listed in Tables 6 and 7.

TABLE 6. Charge transfer wavelengths of PhR with TCNE in CH_2Cl_2 and solvolytic rate constants for RCH_2X[a]

R	*t*-Bu				
λ(nm)	438	475	505	485	510
k_{rel}	1	5×10^4	1.1×10^7		3×10^7

[a] Ref. 53.

TABLE 7. Charge transfer wavelengths of PhR with TCNE in CH_2Cl_2 and σ_p^+ constants[b] of substituents

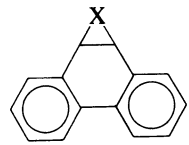
R	H	Me	Et	*i*-Pr	*t*-Bu	*'c*-Pr	Ph	OMe	OH	$CH{=}CH_2$	OPh	NHAc	NMe_2
λ (nm)	387	411	412	415	415	470	498	507	481	480	495	480	520
σ_p^+	0	−0.31	−0.30	−0.28	−0.26	−0.48	−0.18	−0.78	−0.90	−0.16[c]	−0.50	−0.65[d]	−1

[a] Ref. 52.
[b] Ref. 54 unless noted.
[c] Ref. 55.
[d] Ref. 56.

As seen in Table 6 there is a correspondence between the solvolytic rate constants and the charge transfer frequencies. It is notable that the more highly substituted cyclopropyl rings show enhancements in both the rate constants and the CT frequencies.

There was a correlation suggested between the CT frequencies and the σ_p^+ constants[54] shown in Table 7, although there were some deviations noted. However, as can be seen from inspection of the data the linear correspondence is inexact, particularly when some more recently determined σ_p^+ values are included[55, 56]. However, these results clearly identify the π-donor ability of cyclopropyl group in a variety of systems.

The diminished electron-donating ability of the 2,2-dichlorocyclopropyl substituent noted in Section II.F was also observed in charge transfer spectra by Shudo and Okamoto[57], who measured the wavelengths of the TCNE absorptions with substituted cyclopropyl groups for **18**-TCNE. The lower energy CT band for the unsubstituted cyclopropyl derivative relative to the dihydrogen derivative is consistent with stabilization



(18)

X:	CH_2	H,H	CCl_2
$\lambda_{max}^{TCNE\text{-}18}$ (nm)	601	566	546

of positive charge in the excited state by cyclopropyl, and the fact that the dichlorocyclopropyl derivative absorbs at lower energy indicates that in this situation this group is even poorer at stabilizing the excited state than hydrogen.

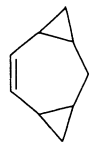
The ionization potentials of a number of cyclopropylalkenes have been measured using photoionization or photoelectron spectroscopy[26, 58–67], and some of these data are summarized in Table 8. It was proposed by Eaton and Traylor[60] that these values could be used as a quantitative measure of the π-donor ability of cyclopropyl to the radical cation resulting from ionization. As can be seen from the data in Table 8 there is a cumulative, but not strictly additive, reduction in the ionization potentials relative to a standard such as 2-butene (9.13 eV)[58], as the number of cyclopropyl groups increases.

TABLE 8. Ionization potentials (eV) of cyclopropylalkenes[a]

c-PrCH = CH_2	*c*-Pr_2C=CH_2	$(c\text{-Pr})_2$C=CHPr-*c*	$(c\text{-Pr})_2$C=C(Pr-*c*)$_2$
9.2,[59, 65] 9.15[64]	8.08, 8.87[61]	7.48	7.25[63]
E-*c*-PrCH=CHPr-*c*	*Z*-*c*-PrCH=CHPr-*c*	$(c\text{-Pr})_2$C=CMe_2	*c*-PrCMe=CH_2
7.72	7.70	7.82	9.12[26,61] 8.92[60]

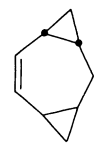
(19)

8.72[60]



(20)

9.0[62]



(21)

8.5[62]

[a] Ref. 58 unless noted.

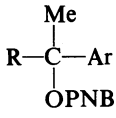
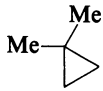
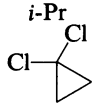
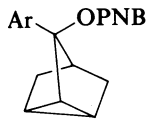
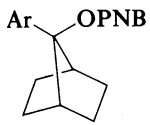
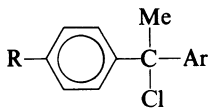
The lower IP for the conformationally fixed derivative **19** compared to *c*-PrCMe=CH_2 is evidence that bisected geometries have the greatest interactions in the ionized states. Similarly, the lower IP for **21**, in which one has bisected cyclopropyl, compared to **20**, in which both groups are perpendicular, provides further evidence for this effect[62].

H. ρ^+ Values

Another way in which the electron-donating ability of cyclopropyl is manifested is in the influence of this group on the sensitivity of reaction centers to the effect of other substituents. This is conveniently examined in carbocation forming reactions by the ρ^+ values which measure the dependence of the reaction to the electron-donating ability of aryl substituents as expressed by their Brown–Hammett σ^+ values by the relation $\log k/k_H = \rho^+\sigma^+$ [54], as shown in Table 9[50, 67, 68].

The ρ^+ value in the 2-substituted-2-aryl-derivatives **22** is -4.76 for R = *i*-Pr, little different from the value of -4.54 for R = Me, but when R is *c*-Pr there is a major reduction to -2.78. This result is reasonably explained[67] as resulting from a strong stabilization of the carbocation center by the cyclopropyl group with a concomitantly lower electron demand on the aryl substituent and hence a lower magnitude of ρ^+. When R is 2,2-dimethylcyclopropyl ρ^+ is -2.06, indicating a greater stabilization of the cation, but when R is 2,2-dichloro ρ^+ is -4.99, showing an even greater dependence than when R is

TABLE 9. The effect of cyclopropyl groups on ρ^+ values

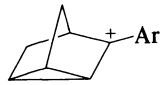
	R	ρ^+
 (22)		-2.06[50]
	c-Pr	-2.78[50]
	i-Pr	-4.76[50]
		-4.99[50]
 (23)		-3.27[67]
 (24)		-5.27[67]
 (25)	c-Pr	-2.24[68]
	i-Pr	-2.91[68]

OPNB, *p*-nitrobenzoate.

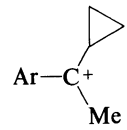
Me. These results thus qualitatively follow the trends of the σ_p^+ values of substituted cyclopropyl groups outlined in Section II.F.

The change in ρ^+ for the comparison of the nortricylyl system (**23**) relative to **24** is comparable to that observed for **22**, indicating that the same attenuation of ρ^+ in the presence of the cyclopropyl group occurs here as well. When the position of the substitution is made more remote, as in the diarylethyl system (**25**), the influence of the substituent is not so great but the same trend is followed[68].

As discussed in Section II.F the ^{13}C-chemical shifts of the cationic carbon of 2-aryl-2-propyl cations (**13**) were used to derive σ^{C^+} constants for substituents, and the shift for the *p*-*c*-Pr substituent indicated a powerful upfield shift caused by this group. The plots of these σ^{C^+} values for a number of other systems versus the changes in chemical shifts ($\Delta\sigma^{C^+}$) give linear plots with ρ^{C^+} values in the range -14.6 to -18[69]. However, for certain other systems such as **26** and **27** these plots are still linear for good electron-donor substituents but give curvature for the poorer donors.



(26)

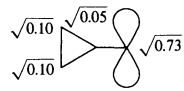


(27)

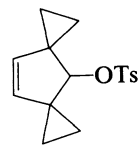
The reasons for the upward curvature for these systems with poorer electron donors is controversial[69, 70] but there appears to be agreement that the linear portions of these plots are related to the π-donation by the substituted aryl groups to the carbocation center. Significantly the ρ^{C^+} values for the linear portions of the plots for **26** and **27** are -11.5 and -10.5, respectively, indicating a significant attenuation of this parameter in these cyclopropyl-substituted systems[69]. Thus just as in the solvolysis rates the effect of cyclopropyl on ρ^{C^+} values is indicative of the strong π-donor ability of this group.

I. Transmission of Substituent Effects

The possibility that conjugation can be transmitted through a cyclopropyl ring as for a vinyl group has attracted a great deal of attention, and there has been evidence cited for a contribution from this effect[71–76]. However, the consensus appears to be that this effect is small[40, 77–79]. A simple explanation advanced[78] for the relative unimportance of such transmission of conjugation is based on CNDO calculations for 2-substituted cyclopropylcarbinyl cations. As shown, the LUMO of the unsubstituted cation has small coefficients at C(1)–C(3) so the π-interaction by substituents at these positions is small.

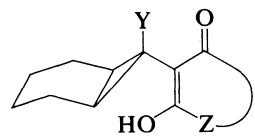


Rate effects due to cyclic conjugation in the generation of a cation from **28** could also not be detected[80].



(28)

A series of 1,1-disubstituted cyclopropanes (**29**) has been reported and, while hydrogen-bonding interactions between the two geminal substituents were observed, no evidence for through conjugation involving the cyclopropyl ring was noted[81].



(29)

III. HETEROATOM-SUBSTITUTED CYCLOPROPANES

A. General Survey

A consistent basis for the understanding of the interaction of cyclopropyl with the second-row substituents is provided by detailed theoretical study[82-84], including 4-31G basis set MO calculations[82]. Optimized geometries and energies were obtained for the substituents Li, BeH, BH_2, CH_3, NH_2, OH, and F, and stabilization energies (SE) were obtained relative to the corresponding *i*-PrX derivatives according to equation[82a]. The results are shown in Table 10.

$$i\text{-PrX} + c\text{-PrH} \rightarrow i\text{-PrH} + c\text{-PrX} \tag{5}$$

TABLE 10. Stabilization energies for substituted cyclopropanes according to equation 5

X	Li	BeH	BH_2[a]	BH_2[b]	CH_3	NH_2	OH	F
SE (kcal mol^{-1})	−6.2	−6.8	−9.1	−1.3	−0.8	−1.0	2.8	6.5

[a] Bisected. [b] Perpendicular.

The results were analyzed in terms of π and σ effects on the assumption that the groups H and F do not have a significant π contribution and thus could be used to define a straight line for the σ effects in a plot of the SE according to equation 5 versus the Pauling electronegativities of the groups (Figure 2). A linear plot of the values for SE energies of 2-propyl-substituted derivatives versus the Pauling electronegativities confirmed that for acyclic alkanes these quantities were directly related.

The deviations from the straight line in Figure 2, all of which are in the direction of greater stabilization, can thus be assigned to π effects. The displacement of the points for Li, BeH and BH_2 (bisected) are thus straightforward examples of π-donation by the ring to a vacant acceptor orbital on the substituent, analogous to the situation depicted in Figure 1 ($\theta = 0°$). The large difference between bisected and perpendicular BH_2 is particularly informative, as it shows these substituents behave in an analogous fashion to the thoroughly investigated CH_2^+ substituent.

Substituents that do not have vacant acceptor orbitals for π-donation from cyclopropyl and yet still show significant stabilization energies are NH_2 and OH[82a]. However, the geometrical consequences of attachment of these substituents is different; e.g. for Li, BeH, and BH_2 (bisected) the distal (C(2)–C(3)) bond is shortened and the vicinal (C(1)–C(2) and C(1)–C(3)) bonds are lengthened, whereas for NH_2 in the favored *anti*-arrangement the cyclopropyl geometry is practically unchanged. It was proposed[82a, 85] that for this compound there is π-donation of the NH_2 lone pair to the 4e′ LUMO of cyclopropane, as depicted in Figure 3. This orbital is antibonding at C(1)–C(2) and C(1)–C(3) and bonding at C(2)–C(3), so this interaction would tend to lengthen the former bonds and shorten the latter. This counteracts an opposite trend due to σ-withdrawal by the substituent and the net result is that the geometry is unchanged.

For the OH and fluoro substituents shortening of the C(1)–C(2) and C(1)–C(3) bonds and lengthening of C(2)–C(3) was indicated by the 4-31G calculations[82a]. It was proposed that this effect results from σ-electron withdrawal from a 1e″ orbital of cyclopropane that is antibonding between C(1)–C(2) and C(1)–C(3) and bonding between C(2)–C(3) and so would give rise to this effect. No evidence for π-donation by fluorine was observed, but the stabilization indicated for OH (Figure 2)[82a] and the preference for the gauche geometry for this substituent indicates that the interaction shown in Figure 3 may also be significant for this substituent[82a]. The geometrical changes for both the OH and F substituents are

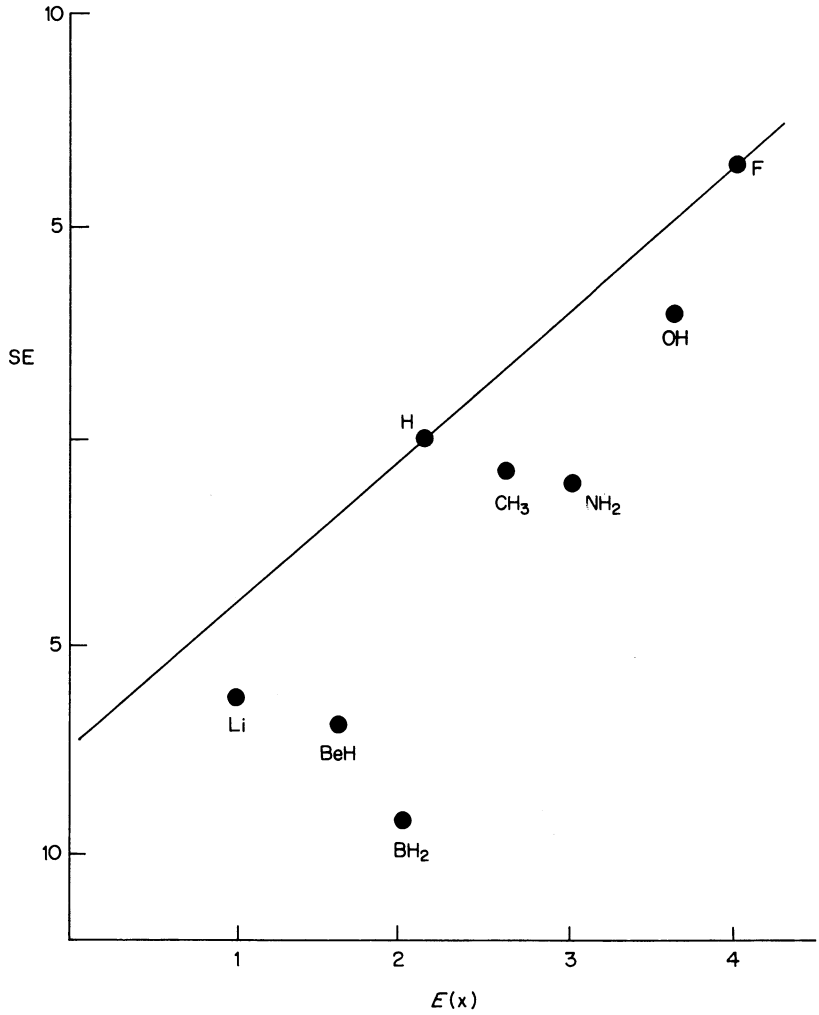


FIGURE 2. Stabilization energies SE (kcal mol^{-1}) for *c*-PrX Compared with *i*-PrX (equation 5) vs. electronegativity $E(x)$

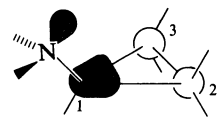


FIGURE 3. Bonding of the NH_2 lone pair to the 4e′ LUMO of cyclopropane

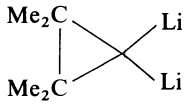
analogous to those for the corresponding 2-propyl derivatives and are not indicative of any conjugative effects involving cyclopropyl[82a].

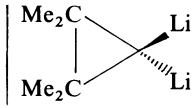
Further 4-31G[82a,b] and 631G*/4-31G[82c,d] basis set calculations on the structures and energies of substituted cyclopropanes emphasize the complex interplay of σ and π interactions of cyclopropyl rings with substituents.

B. Metal Substituents (Groups I–III)

Recent theoretical studies on cyclopropyllithium are in agreement that there is shortening of the C(2)–C(3) and lengthening of the C(1)–C(2) and C(2)–C(3) bonds and while σ effects place considerable electron density from the C–Li bond on the ring there is also a substantial back-donation to the metal[82, 85a].

1,1-Dilithio-2,2,3,3-tetramethylcyclopropane displays only a singlet at δ 1.13 for the ^{1}H NMR of the four methyl groups, indicating a symmetrical structure, but either the planar or tetrahedral structures shown are consistent with this result[85b].





For cyclopropylboron compounds, the initial search for π-donation from cyclopropyl to boron using ^{1}H, ^{11}B and ^{19}F NMR as well as UV spectroscopy did not provide any evidence for a preference for a bisected conformation for the cyclopropyl[86]. Furthermore, tricyclopropylboron was a stronger Lewis acid than triisopropylboron in the formation of complexes with amines and phosphines[86]. This latter behavior would be favored not only on steric grounds due to the presumed smaller size of cyclopropyl but also due to σ-withdrawal by cyclopropyl, but π-donor effects of cyclopropyl would decrease the Lewis basicity.

In contrast to these results, in a more recent study cyclopropyldifluoroborane was assigned the bisected conformation on the basis of microwave, IR, Raman and NMR spectra, with a barrier to rotation of 4.23 kcal mol^{-1} [87]. These results indicate that there is significant π-donation from cyclopropyl to boron, but not enough to cause restricted rotation around the C–B bond to be observable at the temperatures (−100 °C) of the prior NMR studies[86].

C. Group IV Metalloid Substituents

Cyclopropylsilanes are of increasing interest as synthetic intermediates[88] but the understanding of the electronic properties of these compounds is far from complete. Thus for several cyclopropylsilanes (**30**) the vibrational and NMR spectra were interpreted as indicating p(π)–d(π) electron donation from cyclopropyl to silicon[89–92]. The rotational spectrum of cyclopropylsilane was interpreted as indicating a shortening of the C(2)–C(3) bond as predicted for this effect, with a rotational barrier around the C–Si bond of at least 1.95 kcal mol^{-1} [91]. Furthermore the electronic spectra of charge transfer complexes of **30**[93] and some ring- and silicon-substituted derivatives were also interpreted as indicating this effect. However, contrary to these conclusions it was suggested on the basis of theoretical calculations that the interaction was not π-donation to silicon but rather electron donation from silicon to cyclopropyl[94].

c-PrSiR$_3$

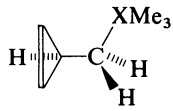
30a, R=H

30b, R=Me

30c, R=Cl

The IR frequencies of **30a** and *c*-PrGeH$_3$ were used to determine σ^* constants for *c*-Pr, and indicated this group to be electron donating[38], contrary to other results based on IR[37] but in agreement with a polarographically obtained value[39]. As noted before the generality of these conclusions is open to question.

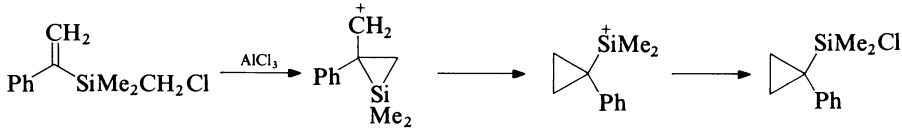
In the structure **31** (X = Si) strong electron donation from the Si–C bond to cyclopropyl was proposed to occur based on the electronic spectra of charge transfer complexes[93] and IR and Raman spectra[90] and a similar interaction for the Sn analog was deduced from the UV photoelectron spectrum and proposed to involve the conformation indicated[95]. Structural studies of these compounds to determine if these conformations are actually favored could be most informative, as would investigation of conformationally fixed compounds and detailed theoretical calculations.



X = Si, Sn

(31)

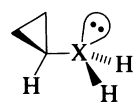
Reaction of vinyl(chloromethyl)silanes such as **31a** led to cyclopropylsilane derivatives **31d**, and intermediates such as **31b** and **31c** were implicated, although an understanding of the delocalization in the cationic intermediates and the cyclopropylsilanes is still under development[95a].



(31a) **(31b)** **(31c)** **(31d)**

D. Nitrogen and Phosphorous Substituents

Cyclopropylamine[96, 97] and cyclopropylphosphine[98] have been proposed on the basis of their microwave spectra to have the conformation **32** with a plane of symmetry bisecting the H–X–H angle and the plane of the cyclopropane ring. This geometry is consistent with the interaction shown in Figure 3 involving electron donation to the 4e′ LUMO of cyclopropane by the nitrogen lone pair[82, 85]. The predicted geometry is that found experimentally, although the measurement of the thermochemistry of the interaction in this compound did not reveal any significant stabilization (Section II.E, Scheme 1)[24].



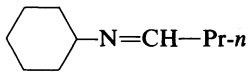
X = N, P

(32)

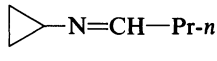
There also appear to be major differences of opinion in the interpretation of the calculational results by Schleyer and coworkers[82] and by Durmaz and Kollmar[99]. The latter concluded: 'The cyclopropyl ring is a poor π-electron acceptor. Hyperconjugation with neutral π-donating substituents seems to be of little importance. The ring structure of

cyclopropanes with electronegative substituents is also not determined by the σ-electron acceptor ability of the substituent.' However, the arguments adduced for donation to the 4e' LUMO by the NH_2 group appear persuasive as determining the structure of this compound, but the thermochemical effects are worthy of further investigation.

The UV spectra of the imines **33–36** show a shift to longer wavelength for the cyclopropyl compounds **34** and **36** compared to the cyclohexyl and *n*-butyl analogs **33** and **35**, respectively[100]. This was attributed to an interaction of cyclopropyl with the nitrogen lone pair in **34** affecting the $n \rightarrow \pi^*$ band, and π-donation of cyclopropyl in **36** to affect the $\pi \rightarrow \pi^*$ band.



(**33**)



(**34**)

λ_{max}^{hexane} 224–230 nm (log ε 2.26)

λ_{max}^{vapor} 214 nm (log ε 2.74)

n-BuN=CHPh

(**35**)

λ_{max}^{EtOH} 235 nm (log ε 4.03)

234 nm (log ε 2.43)

226 nm (log ε 2.59)

c-PrN=CHPh

(**36**)

λ_{max}^{hexane} 252 nm (log ε 4.16)

Nitrocyclopropane has been found to prefer the bisected conformation by both theoretical[101] and experimental (microwave)[102] studies, consistent with π-electron donation by cyclopropyl to the p orbital on nitrogen. Similar results have been obtained for nitrosocyclopropane[103, 104].

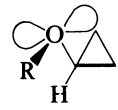
The possibility of electron donation by cyclopropane to an electron-deficient phosphorous in a highly substituted phosphate for which the X-ray structure is available unfortunately cannot be properly assessed because the heavy substitution on the ring obscures the interpretation of the observed bond lengths and angles[105].

Enhanced rates of solvolysis of *c*-PrP(=O) (Ph) NHPh relative to acyclic analogs were interpreted as possibly reflecting positive charge development in the rate-limiting transition states, but the importance of steric effects could not be discounted[106]. Thus there is no firm evidence for electron donation by cyclopropyl to positively charged phosphorous[105, 106].

E. Oxygen and Sulfur Substituents

The experimentally determined conformations of both cyclopropanol[107] and cyclopropyl methyl ether[108] are in the gauche form (**37**). This geometry would permit electron donation from an oxygen lone pair to the 4e' LUMO of cyclopropane as shown in Figure 3, and it has been predicted by 4-31G calculations[82] that this geometry would be favored and contribute some stability to the molecule.

A geometry similar to **37** was found experimentally by microwave spectroscopy for *c*-PrSMe[109]. As yet a comparison of the efficiency of overlap of oxygen and sulfur lone pairs with the 4e' LUMO of cyclopropane has not appeared.



(37)

F. Halogen Substituents

There have been a number of recent theoretical and experimental studies of the structures of halocyclopropanes[82, 110–115], with two particularly useful summaries[82, 115]. Some of the results collected in these references are listed in Table 11.

TABLE 11. Bond lengths (Å) in 1,1-disubstituted cyclopropanes[a]

	H,H	H,F[b]	F,F	H,Cl	Cl,Cl
C(1)–C(2)	1.510	1.480	1.470	1.516	1.496
C(2)–C(3)	1.510	1.505	1.552	1.524	1.529

[a] Averages of data reported in Ref. 115 unless noted. Results were obtained by microwave, electron-diffraction, and theoretical methods, with substantial agreement between methods for individual compounds.
[b] 4-31G calculations from Ref. 82. Values for both distances are somewhat shorter than those in Ref. 115 but there is agreement that the C(2)–C(3) bond is significantly longer than the C(1)–C(2) bond.

The structures of halocyclopropanes are significantly influenced by the halogen, as illustrated with the bond length data in Table 11 (data for particular compounds obtained by different methods as noted are in reasonable agreement, so average values are given). These trends were interpreted[115] as resulting from strong σ-electron withdrawal from the ring in the case of the fluoro compounds from an orbital which is antibonding in the C(1)–C(2) region and bonding in the C(2)–C(3) region, so that the former bond is shortened and the latter lengthened. π-Electron donation was negligible[82, 112]. However, for monochlorocyclopropane σ-withdrawal is small and there is a π-donation from the chlorine to an antibonding ring orbital which causes lengthening of all the C–C bonds. The slightly greater length of the C(2)–C(3) bond is due to the σ effect. In 1,1-dichlorocyclopropane the π effect is not significant because of mutual interactions of the chlorines and the σ effect is operative as in the difluoro compound, but is not as strong[115]. A test for conjugative effects in chlorocyclopropanes using nuclear quadrupole resonance was inconclusive[116a].

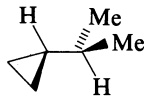
The structures of *cis*- and *trans*-1,2-difluorocyclopropane obtained from their microwave spectra[116b, c] are in general agreement with theoretical studies[114].

IV. CARBON-SUBSTITUTED CYCLOPROPANES

A. Saturated Carbon Groups

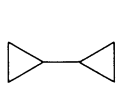
Structure determinations of alkyl-substituted cyclopropanes have been carried out by microwave spectroscopy[85], NMR[117], theoretical methods[82, 118], Raman[119] and photoelectron spectroscopy[62, 65, 120]. Rotational barriers around the C–C bond from the ring to the substituent are observed, but these are rather small and do not appear to arise from any

significant electron delocalization between the ring and the substituent. Thus isopropylcyclopropane was found by ^{1}H-NMR to have about a 2 to 1 preference for the *trans* geometry (**38**), a result predicted by molecular mechanics calculations[118].

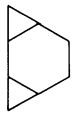


(**38**)

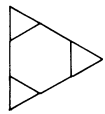
There has been a great deal of attention devoted to the structure of bicyclopropyl (**39**)[119, 120], conformationally restrained bicyclopropyls such as **40**[62] and tricyclopropyls such as **41**[62] and **42**[65]. There is agreement that there is conjugative interaction between the



(**39**)



(**40**)



(**41**)

(**42**)

cyclopropyls in agreement with theory, but the nature of the interactions is subtle. The topic is discussed extensively in other reviews[4, 121] and chapters of this volume.

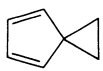
B. Cyclopropylalkenes

These compounds have been studied for a long time and there is a great deal of recent evidence from UV studies[13, 17], photoelectron spectra and ionization potentials[58–65], Raman spectroscopy[119, 122], alkene equilibration[25, 26], microwave spectroscopy[85], X-ray[21, 22] and theoretical studies[123–125] that there is conjugation between vinyl and cyclopropyl, particularly in the bisected conformation.

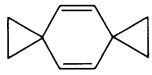
The stabilization energy for this conformation relative to the gauche arrangement has been measured as 1.24 kcal mol^{-1} [122], as opposed to a calculated value of 2.76 (3-21G basis set)[124].

In an equilibration study the conjugated vinylcyclopropane **11b** was more stable than the unconjugated isomer **11a** by 1.2 kcal mol^{-1} [25].

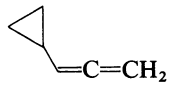
Two 1,1-divinylcyclopropanes that have attracted a great deal of interest are **43** and **44**. The microwave structure of the first has been obtained[126] and, based on the photoelectron spectrum[65] and STO-3G calculations[126], a strong electron delocalization from the ring has been implicated[126]. Conjugation was also present in **44**, but through conjugation of the cyclopropyls was not prominent[66]. Cyclopropylallenes such as **45** behaved similarly to vinylcyclopropanes, with no evidence for interaction of the cyclopropyl with the second double bond[61].



(**43**)



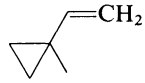
(**44**)



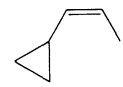
(**45**)

In a theoretical study using MNDO/3 it was concluded that introduction of a methyl group on vinylcyclopropane at either the 1-position of the cyclopropyl as in **46** or the *cis*-2-

position of the double bond to give **47** would cause a 30° rotation of the double bond from the bisected conformation to relieve steric crowding[127a]. Similar studies were carried out for arylcyclopropanes[127a].

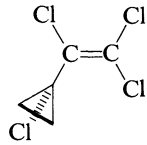


(**46**)



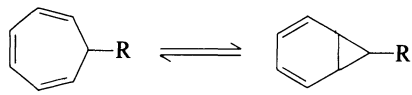
(**47**)

1-Chloro-1-(trichlorovinyl)cyclopropane (**47a**) adopts a perpendicular conformation, as revealed by an electron diffraction study[127b]. This result provides further evidence that steric influences can prevent formation of the usually favored bisected conformation.

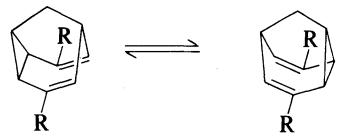


(**47a**)

Fluxional molecules involving cyclopropylalkenyl systems have been extensively studied, and while a full discussion of this voluminous work is beyond the scope of this review two examples of current interest are shown (**48**[128] and **49**[129]). The effect of the substituent R on the equilibrium and rate constants, respectively, were of particular interest in these studies. Other recent studies of such systems have appeared.[130, 131].



(**48**)



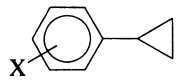
(**49**)

C. Cyclopropylarenes

As noted in Section II.E there is thermochemical evidence for a stabilizing interaction in cyclopropylbenzene[24] and the UV spectra of conformationally fixed cyclopropylarenes show that lower energy absorption occurs in the bisected conformation[13–15]. However, the X-ray structures showed the majority of the available examples were in the perpendicular conformation (**10**)[22].

The ^{13}C-NMR chemical shifts of the C(2)–C(3) cyclopropyl carbons in a series of cyclopropylarenes (**50**) correlated with the σ values of the substituents with a slope of 2.0,

as compared to slopes of 6.5, −0.9 and −0.7 for the β-carbons of styrenes, arylethanes, and 1-arylpropanes, respectively[132]. These results were interpreted in terms of conjugative electron donation from cyclopropyl to the aryl ring, but the effect was not as strong as the corresponding donation from the vinyl group in styrenes[132].



(50)

Cyclopropylbenzene was calculated at the STO-3G level (without geometry optimization) to have a 4.3 kcal mol^{-1} barrier to rotation with a preference for the bisected conformation (**51**)[133], and the NMR coupling constant between the *p*-hydrogen and the methine hydrogen was interpreted in terms of a 2.0 kcal mol^{-1} barrier[133]. The Raman spectrum was estimated to indicate a 5.8 kcal mol^{-1} barrier[134], but this value has been criticized as being too high[133]. The photoelectron spectra of substituted cyclopropyl derivatives (**51**)[135] showed little effect of the substituent R on the spectra and since large groups were felt to require the perpendicular conformation (**10**) it was argued that all of the compounds studied, including when R = H, had little conjugation between phenyl and cyclopropyl and existed in conformation **10**[135].

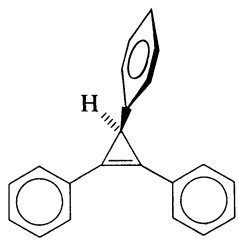
R = H, Me, Et, *i*-Pr, *t*-Bu
X = H, Cl, MeO

(51)

The microwave spectrum of *p*-cyclopropylbenzaldehyde (**51**, R = H, X = CHO) indicated a very low barrier to rotation for the cyclopropyl group[136]. Interestingly this was interpreted as to 'not necessarily imply a lack of conjugation but rather that the various factors contributing to the potential barrier nearly cancel'[136]. These various factors were not specified.

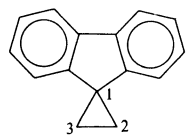
The conformations of a further series of ring-substituted cyclopropylbenzenes and 1-methylcyclopropylbenzenes were assigned based on the shielding of the aryl hydrogens by the cyclopropyl rings[137]. For the cyclopropyl compounds the bisected (**51**) and the perpendicular (**10**) conformations were proposed to be in equilibrium, whereas with the 1-methylcyclopropyl derivatives steric factors enforced the perpendicular geometry, despite the electronic preference for the bisected form[137a].

The X-ray structure of 1,2,3-triphenylcyclopropene showed a preference for the bisected geometry **51a** of the 3-phenyl and a coplanar arrangement for the 1- and 2-phenyls[137b].

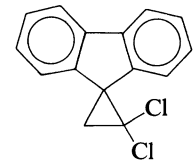


(51a)

The X-ray structures of the fluorene derivatives **52** and **53** showed that **52** had a distal (C(2)–C(3)) bond of 1.496 Å that was significantly shorter than the vicinal (C(1)–C(2) and C(1)–C(3)) bonds at 1.531 Å[138]. Thus this structure is a dibenz analog of **43** (Section IV.B). The structural distortions in the cyclopropane ring in **43** and **52** are the same, and evidently arise in both cases from π-donation from cyclopropyl to the aromatic system.



(52)



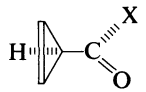
(53)

In the 2,2-dichloro analog(**53**) the C(2)–C(3) bond is still the shortest at 1.475 Å and the C(1)–C(2) and C(1)–C(3) bonds are 1.537 and 1.517 Å, respectively. In 1,1-dichlorocyclopropane the bonds to the chlorine-substituted carbon are shorter, whereas in **52** the C(1)–C(2) bond is longer than C(1)–C(3). Steric effects were rejected as a possible cause of this effect, but no other reasonable explanation was put forward[138].

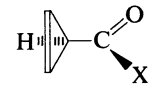
Taken together the extensive evidence on the role of conjugation in cyclopropylbenzenes does not provide a consistent picture of either the preferred conformation or the importance of conjugation in these derivatives. The consensus is that substituents R larger than H on the 1-position of the cyclopropyl give a significant preference for the perpendicular conformation, but the situation when R is H appears ambiguous.

D. Cyclopropyl Carbonyl Derivatives

The molecular structures of compounds of the type *c*-PrCOX all show a preference for bisected geometries, with both the *cis* (**54**) and *trans* (**55**) geometries being observed[139–146].



(54)



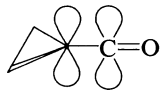
(55)

Thus for X = F studies using ^{19}F-NMR[139] and IR Raman spectroscopy[140] indicated the presence of these two conformers, with rotational barriers of 5.5 kcal mol^{-1} in solution[139] and 6.20 kcal mol^{-1} in the gas phase[140]. The *cis* form is more stable in the gas phase by 629 cal mol^{-1}, while the *trans* form is more stable by 263 cal mol^{-1} in solution[140]. The latter effect was attributed to intermolecular interactions[140].

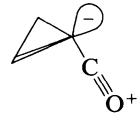
For X = Cl[141, 142] the *cis* form predominated in the gas phase or solution but only the *trans* was observed in the solid. The *cis* conformation was also more stable for X = Me[143] but for X = H the experimental results are at odds, with microwave results favoring the *trans* structure[144] whereas electron diffraction predicts the *cis* rotamer to be more stable[145]. Theoretical studies favor the *cis* isomer[125, 146] and also suggest there is an attractive interaction between the carbonyl group and the two proximal adjacent hydrogens in the *cis* conformer[146]. This latter finding provides a possible cause of the general preference noted for the *cis* conformer.

Calculations also favor a bisected geometry when X = OH[125].

Cyclopropylidenemethanone (**56**) is a ketene whose structure has been examined by microwave spectroscopy[147]. Interestingly this molecule is not planar (C_{2v} symmetry) as in **56a** but oscillates between two bent forms with potential minima at 17.5° from the ring plane that have the dipolar contributions shown in **56b**. The relative efficacy of π-donation from the ring to the carbonyl group in **56a** and **56b** is yet to be elucidated.



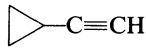
(**56a**)



(**56b**)

E. Cyclopropylalkynes

Two recent studies of cyclopropylacetylene (**57**) using microwave[148] and a combination of microwave and electron diffraction[149] gave results that were in reasonable agreement. The average bond lengths of the two studies showed the distal (C(2)–C(3)) bond to be distinctly shorter at 1.496 Å than the vicinal (C(1)–C(2)) bond at 1.526 Å, and the C(1)–C(4) bond (1.434 Å) was short. Only in the latter case was the difference of the two reported values greater than the sum of the reported uncertainties. These values are as expected for π-donation from cyclopropyl to the alkyne.



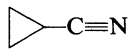
(**57**)

However, another recent study of **57** based solely on electron diffraction could not detect differences in the ring C–C distances[150]. These results were discounted[149] on the basis that the method used was unreliable to fully resolve the structure.

It was also concluded on the basis of an analysis of bond lengths in several related compounds that cyclopropyl is a better π-donor to C≡CH than is vinyl[149].

F. Cyclopropyl Cyanide

The structure of cyclopropyl cyanide (**58**) has been examined by microwave spectroscopy[148, 151], Raman spectroscopy[152], and theoretical methods[123] and the structure is very similar to cyclopropylacetylene (**57**). The C–C bond distances (Å) determined by the most recent microwave examination for **58** of C(1)–C(2) (1.529), C(2)–C(3) (1.500) and C(1)–C(4) (1.420) are identical within the experimental uncertainty with those for **57**[148]. The calculated geometry[123] for **58** is also in reasonable agreement with the experimental structure.



(**58**)

A number of substituted cyclopropyl cyanide structures have been determined by X-ray and these are also consistent with strong π-donation by cyclopropyl[22].

Just as in the case of **57** it was suggested that cyclopropyl was a better conjugating group than vinyl in donating to the cyano group[148]. However, in the study of X-ray structures it was observed that the average C–CN bond lengths for vinyl cyanides were shorter than that for cyclopropyl cyanides[22], but this was discounted[148] as evidence bearing upon which group was the better donor because the substrates in the X-ray study bore other substituents which complicated the interpretation.

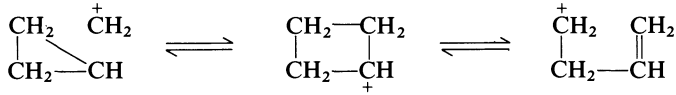
V. CYCLOPROPYLCARBINYL CARBOCATIONS

A. $C_4H_7^+$

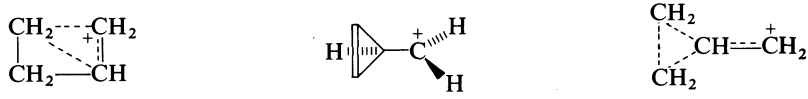
The structure of the cyclopropylcarbinyl cation has remained one of the most subtle and elusive questions in organic chemistry, and despite the increasingly more sophisticated experimental and theoretical techniques applied to this question there are still unresolved questions regarding this species.

This problem was originally investigated by solvolysis studies, and the structure of the intermediate ion and the nature of the delocalization was inferred from rate and product studies, which made extensive use of isotopically labeled substrates. These earlier studies have been thoroughly reviewed[153–155].

As pointed out[156] by the pioneer in those studies $C_4H_7^+$ 'has some of the characteristics expected for a very rapidly equilibrating mixture of classical cyclopropylmethyl, cyclobutyl, and 3-butenyl cations and yet other characteristics which wholly belie any description that implies conventional charge distributions or geometries derived from structural representations using solid lines representing two-electron bonds'. The rapidly equilibrating ions referred to are shown in **59a**, **59b** and **59c** respectively, and the structures with unconventional charge distribution are the bicyclobutonium ion (**60**) or the bisected structure (**61**).



(59a) **(59b)** **(59c)**



(60) **(61a)** **(61b)**

The bicyclobutonium ion (**60**) or the bisected structure (**61**) would both exist as a rapidly equilibrating group of three structures which would render the three CH_2 groups equivalent over a short time span, a result well-documented by the ^1H- and ^{13}C-NMR spectra of the long-lived ions[156–159] and by the scrambling in the products from isotopically labeled derivatives[156–159].

A long-standing controversy has existed over whether structure **60** or **61** is the correct representation of the ion. These ions have fundamentally different symmetry, with all three of the CH_2 groups in unique positions in **60**, but with a plane of symmetry and a pair of equivalent CH_2 groups in **61**.

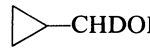
The structure of **61** is usually represented with the valence bond formulation **61a** which

is equivalent to the dotted line structure **61b**. In either representation there is significant electron delocalization from the C–C bonds of the ring.

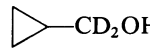
Examination of the ^{13}C-NMR spectrum of $C_4H_7^+$ prepared from cyclopropylcarbinol enriched with 43 % ^{13}C at the carbinol carbon revealed strong temperature dependences of the two signals visible, with a downfield shift of the CH resonance and an upfield shift of the averaged signal for the three CH_2 groups[157]. Even at -155°C the latter signal was not resolved. It was argued that the strong temperature dependences indicated an equilibrium was occurring between two distinct species, and these were assigned the bicyclobutonium and cyclopropylcarbinyl structures **60** and **61** as the lower and higher energy forms, respectively, with an energy difference of 1 ± 0.5 kcal mol^{-1} [157].

Although the CH_2 groups of $C_4H_7^+$ were rapidly equilibrated on the NMR time scale in solution even at -150°C, the interconversion of the CH and CH_2 groups is slow on the NMR time scale even at -61°C. However, a slow equilibration does occur, and it is estimated that this has $\Delta G^{\ddagger}$ greater than 10 kcal mol^{-1}, or at least 5 kcal mol^{-1} more than the value for simple 1,2-hydride shifts in simple secondary carbocations such as cyclopentyl[158].

The NMR spectra of the ions $C_4H_6D^+$ and $C_4H_5D_2^+$, prepared from the carbinols as in equations 6 and 7, showed significant isotopic chemical shifts interpreted as showing



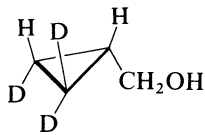
(6)



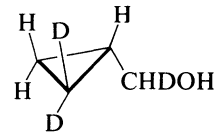
(7)

equilibrating species were involved[159]. The structure was assigned to be a degenerate set of bicyclobutonium ions (**60**) on the basis of the large difference in the CH_2 groups indicated by the isotopic shifts, and it was reasoned that the differences in CH_2 were much greater in **60** than in **61**. It was further suggested[159] that a splitting in the CH peak indicated a further equilibrium with a structurally different ion, and the structure **61** was favored for this species.

Studies[156] of ions derived from stereospecifically ring-deuterated cyclopropylcarbinols **62** and **63** showed that the protons on each CH_2 group were not equivalent and that the proton and carbon chemical shifts were strongly dependent on this stereochemistry. Interconversion of the ions from **62** and **63** was slow at -90°C, corresponding to a barrier of at least 14 kcal mol^{-1}. The chemical shifts have not yet been completely explained but were interpreted as being consistent with the bicyclobutonium ion formulation (**60**)[156].



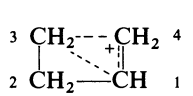
(**62**)



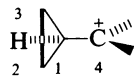
(**63**)

Molecular orbital calculations using 4-31G and 6-31G* basis sets led to the conclusion that the minimum energy structure for $C_4H_7^+$ was the bisected cyclopropylcarbinyl cation **61** (Table 12) with a plane of symmetry defined by the formally cationic carbon[160]. A second structure (**64**) was also found as an energy minimum that was subtly different from **61**, but possessed an unsymmetrical cyclopropyl ring with one corner bent toward the

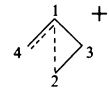
TABLE 12. Calculated bond lengths (Å) for $C_4H_7^+$ structures



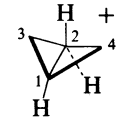
(60)



(61)



(64)



(65)

	61[a]	61[b]	64[b]	65[a]	65[b]
C(1)–C(2)	1.6002	1.664	1.758	1.7137	1.778
C(1)–C(3)	1.6002	1.664	1.522	1.4489	1.435
C(1)–C(4)	1.3651	1.347	1.357	1.4490	1.435
C(2)–C(3)	1.4252	1.412	1.456	1.5796	1.650
C(2)–C(4)			2.427	1.5789	1.650

[a] MINDO/3, Ref. 161. [b] 4-31G, Ref. 160.

carbinyl center[160]. The cyclobutyl cation was calculated to be an energy maximum, and although there was some resemblance of **64** to the bicyclobutonium ion (**60**) it was argued that these were different, specifically in the absence of bonding between C(2) and C(4)[160].

In contrast MINDO/3 calculations suggested both that **61** was an energy minimum, and that a cyclobutyl cation structure (**65**) was not only an energy minimum but was also lower in energy than **61**[161]. Some MINDO calculations on **61** give similar geometries to the MINDO/3 calculations[162].

The C–C bond distances calculated for these structures are compared in Table 12, and it appears that while there is reasonable agreement between the 4-31G/6-31G* and the MINDO/3 calculations for the geometries of both structures **61** and **65**, structure **64**, the second minimum reported by Hehre and coworkers[160] resembles **61** more than it does **65**. The two methods diverge completely in the calculated energy for **65**, which is an energy maximum in the 4-31G/6-31G* calculations and the lowest energy minimum in the MINDO/3 calculation.

There is some harmony between the calculations and experimental results, in that the most recent NMR investigations of $C_4H_7^+$ have been interpreted as showing the coexistence of two different species[156–159]. Furthermore, gas phase reactions of $C_4H_7^+$ with NH_3 or H_2O have been found to produce both cyclopropylcarbinyl and cyclobutyl products[163] and this result was interpreted as showing the simultaneous presence of two structurally different ions[163], although a single ion with two different accessible reaction pathways would also appear possible.

It was further argued[161] that structure **61** could profitably be considered as a π complex between ethylene and a vinyl cation, whereas **65** was considered as a protonated bicyclobutane. Protonation of bicyclobutane was proposed as a likely route to $C_4H_7^+$[161].

A recent study of photoelectron spectra of isomeric C_4H_7 radicals has provided heats of formation of the allylcarbinyl cation (231 ± 3 kcal mol^{-1}) and the cyclobutyl cation (225.1 ± 1.1 kcal mol^{-1}) but the failure of attempts to generate the cyclopropylcarbinyl radical meant that no heat of formation of the corresponding cation could be obtained[164]. Similarly, the heats of formation of geometrically reorganized structures such as puckered cyclobutyl cations and bicyclobutonium ions could not be assigned. Further experiments along these lines are clearly indicated, as well as further calculations to resolve the current dichotomy in the theoretical studies.

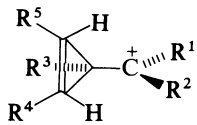
B. Substituted Cyclopropylcarbinyl Cations

Substituted cyclopropylcarbinyl systems that are free to adopt the optimum conformation around the bond from cyclopropyl to the cationic center are considred in this section.

The rate effects of substituents on the cyclopropyl ring are discussed in earlier reviews[153–155] and in Section II. It was particularly notable that these substituent effects appeared to be additive[34, 49, 50] and were interpreted in terms of symmetrical π-donation through a bisected geometry (see Figure 1).

Numerous methyl-substituted cyclopropylcarbinyl cations have been observed by NMR as long-lived species, including **66–74** (Table 13)[165–167]. In the case of **68** there was some dispute about the structure, with both a cyclobutyl cation[170] and a bridged structure suggested[165a]. Study of the deuterated ion favored the latter structure[165b].

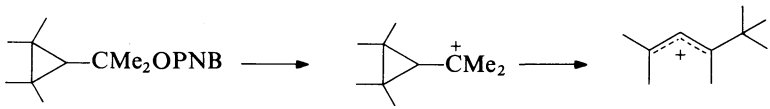
TABLE 13. Methyl-substituted cyclopropylcarbinyl cations



	R^1	R^2	R^3	R^4	R^5	Ref.
66	Me	H	H	H	H	166
67	H	Me	H	H	H	169
68	H	H	Me	H	H	165
69	H	Me	Me	H	H	167[a]
70	Me	H	H	Me	H	168
71	Me	H	Me	Me	H	168
72	Me	H	H	Me	Me	168
73	Me	Me	H	H	H	166
74	Me	Me	Me	H	H	166

[a] Shown as R^1, R^3 = Me in reference 168.

A hexamethylcyclopropylcarbinyl ion (**75**) was generated under solvolytic conditions, but under long-lived ion conditions ring opening to an allyl cation occurred (equation 8)[171].

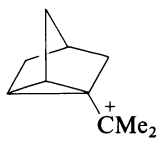


(8)

(**75**)

OPNB = *p*-nitrobenzoate

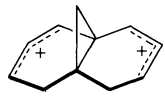
The ion **76** was directly observed by NMR[172] and on the basis of MNDO and STO-3G calculations it was argued that there was a significant contribution from the structure **76a**[162].



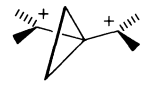
(**76**)

(**76a**)

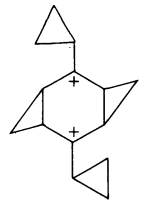
Evidence has also been presented[173] for the existence of a long-lived ion (**77**) containing the dicyclopropyldicarbinyl dication moiety **78**. Related cations including **78a** have also been reported[173b].



(**77**)



(**78**)

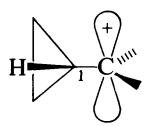


(**78a**)

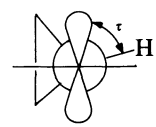
C. Structure and Conformation of Cyclopropylcarbinyl Cations

Equation 9 has been introduced for the assignment of the structure and conformation of cyclopropylcarbinyl cations, by Kelly and coworkers[174–177] and involves the angle τ in **79** between the C–H bond at C(1) of the cyclopropyl group and the unoccupied p orbital of the cationic carbon (the designation of the angle τ here is consistent with the definition of Figure 1, Section II.C, although Kelly and coworkers[174–177] designate this angle as θ). In equation 9, ΔJ is the difference between $^1J_{CH}$ for this proton and that for an appropriate uncharged model ketone or alkene, and A and B are inductive and hyperconjugative parameters, respectively. For the bisected geometry shown, τ is 90° and ΔJ is a maximum.

$$\Delta J = A - B\cos^2 \tau \tag{9}$$

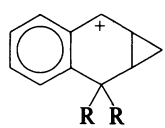


(**79a**)

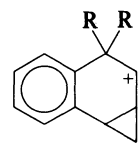


(**79b**)

This equation was used in the assignment of conformation and structure of some benzobicyclo[4.1.0]heptyl cations[177] and it was concluded that the bisected conformation was favored for several model compounds, and for a reported example originally assigned



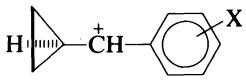
(**80**)



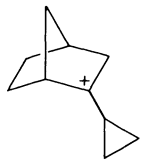
(**81**)

to favor a more perpendicular geometry[178]. It was further suggested[177] that for this latter case that the benzylic structure **80** might be favored rather than **81**, which had originally been proposed[178].

In arylcyclopropylcarbinyl cations of the type **82** it was also found that the electron demand at the carbocation center, as determined by the aryl substituent X, also influenced the ΔJ values, which were correlated by the equation $\Delta J = (1+0.6\sigma^+)(10.9-14.3\cos^2\tau)$[176].



(82)



(83)

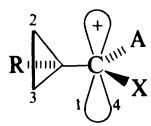
The 2-cyclopropyl-2-norbornyl cation (**83**) was evidently present as two conformers at −90°C due to slow rotation about the bond to the cyclopropyl, but the individual structures could not be assigned[179]. The CH_2 groups of the cyclopropyl group were both deshielded but by different amounts (43.0 and 56.0 ppm), and it was suggested that this indicated more effective donation from one of the C–C bonds of the cyclopropyl[179], which presumably implies a resemblance to the bicyclobutonium structure (**60**), or to structure **64**.

D. Conformationally Restricted Cyclopropylcarbinyl Cations

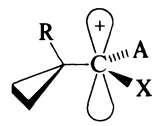
1. Solvolysis studies

Reactivity studies of conformationally fixed substrates has been an important technique for the study of the conjugative stabilization of carbocation centers afforded by cyclopropyl groups, and although Chapter 8 of this monograph is devoted to this topic, brief mention will be made of the subject here because of the direct relevance to the topic at hand. Examination of the long-lived ions themselves, principally by NMR, provides a further dimension to the analysis.

The reactivity of a large number of geometrically constrained cyclopropylcarbinyl cations have been examined so that the angular dependence of the ability of the cyclopropyl group to stabilize the developing carbocation center could be assessed. Overlap is optimal when the angle θ in Figure 1, Section II.C, is 0°, as in **7b**, and is at a minimum when θ is 90°, as in **7d**. Relative reactivities for conformationally fixed systems



(7b)



(7d)

with different values of θ are given in Figure 4[42,180–182] as compiled by Rhodes and DiFate for **84**–**87**[180].

There are several obstacles to precise correlations of geometry with reactivity in the various model systems, of which the most important is that none of the cation geometries is experimentally determined, and in only a few cases are the geometries of the precursors

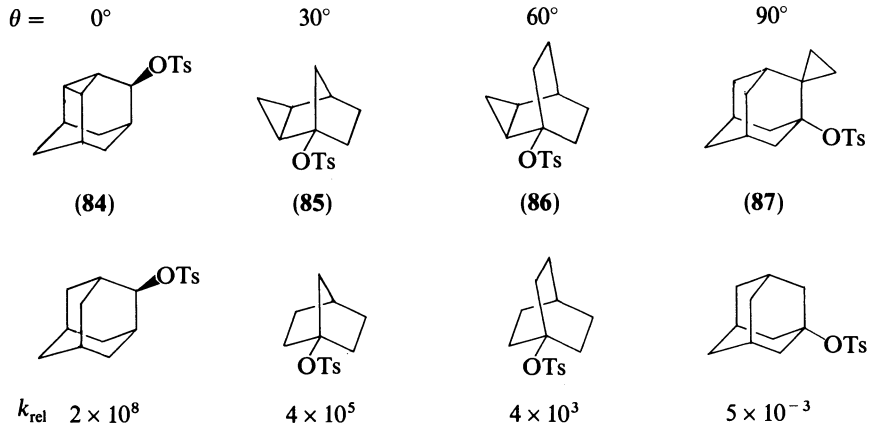
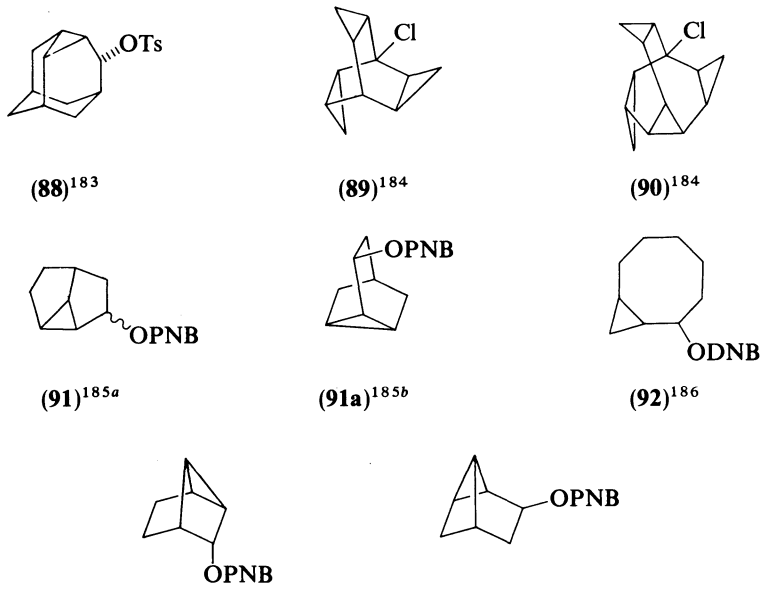


FIGURE 4. Overlap angles and relative reactivities for cyclopropylcarbinyl systems

known. The angles θ have usually been estimated from the known or assumed precursor geometries.

Furthermore, in polycyclic systems the cationic center usually is constrained from achieving a trigonal geometry. The problems with assessing the degree of conjugation in



OPNB = *p*-nitrobenzoate
ODNB = 3,5-dinitrobenzoate

FIGURE 5. Precursors to geometrically constrained cyclopropylcarbinyl systems

such unsymmetrical systems is considered in Section II.C and unequal π-donation by the C(1)–C(2) and C(1)–C(3) bonds is evidently the cause of the difference in chemical shifts of C(2) and C(3) in **83**[179].

The lack of planarity of the carbocation center and the unequal ability for π-donation of the cyclopropyl ring bonds has also been remarked for systems **88–92**[183–186] and presumably holds for others such as **93**[187, 188] and **94**[189a] as well (Figure 5). The triscyclopropyl systems **89** and **90** are notable in that the efficiency of overlap can be estimated from X-ray structures of the reactants[184].

Stabilizing interactions of developing carbocations were observed for one but not both of the β-cyclopropyl groups in **94a–94c**[189b].

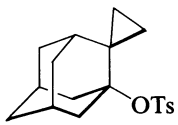
(94a)

(94b)

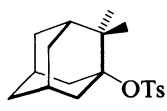
(94c)

2. *Inductive effect of cyclopropyl*

In their study of the solvolysis of tosylate (**87**) Ree and Martin[42] addressed the question of why there was an actual rate deceleration relative to **95** (k (**95**)/k(**87**) = 360) as compared to the rate acceleration of approximately 10^5 for a bisected geometry.



(87)



(95)

These authors pointed out that in the conversion of **87** to a cation there would be some flattening of the ring which would cause extra strain due to the restricted bond angles of cyclopropyl, but concluded that while this would tend to decrease the reactivity, the net effect would be small. The authors then considered that the rate might be due to the inductive effect of cyclopropyl, and utilized three methods for assessing σ_I, namely the OH stretching frequency of cyclopropanol, dipole moment data for cyclopropyl chloride, and the acidity constant of cyclopropylbenzoic acid. The authors suggested the first two of these values would be 'relatively free of contributions from resonance effects 'but as pointed out in Sections III.D and III.E resonance (or π-interaction) of cyclopropyl is strong with both OH and Cl substrates, and it is clear that resonance effects are significant in cyclopropyl interactions with carboxylic acid groups. Thus all three of these measures of σ_I contain resonance components, and cannot be used to assess a purely inductive effect for cyclopropyl. Furthermore the plot of log k versus σ_I published by these authors gave an extremely large magnitude of ρ_I of -36.6, which as the authors pointed out was comparable to those found for gas phase ions. Inspection of their plot shows that in fact the slope of the line defined for methyl and isopropyl is -20, identical to the value quoted[42] for tertiary alkyl chlorides.

In consideration of these results[42] de Meijere concluded[4]: 'the cyclopropyl group has an inductive electron-attracting effect in this case and destabilizes the intermediate carbenium ion'. However, the destabilization referred to is for spiro cyclopropyl relative to a *tert*-butyl

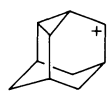
carbon substituent and as noted above there is also a steric component of the rate effect which cannot be quantitatively assessed.

Thus the low reactivity of **87** certainly shows the absence of the strong conjugative stabilization found for the bisected cyclopropylcarbinyl arrangement, but does not provide a quantitative assessment as to the respective roles of ring strain and the inductive effect of cyclopropyl in giving the observed rate of deceleration relative to dimethyl substituents. Accurate molecular mechanics calculations for **87** and the derived cation would provide an assessment of the former, and a measure of σ_I for *c*-Pr free of resonance effects is much to be desired.

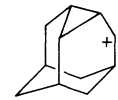
Ree and Martin[42] used the data of Brown and Cleveland[33] to calculate a σ_p^+ value of -0.21 for a cyclopropyl group twisted out of conjugation with the aryl ring by two *ortho*-methyl groups. The σ_m^+ value of -0.03 for cyclopropyl[30] also indicates a cation-stabilizing ability intermediate between H and CH_3 for a non-conjugated cyclopropyl group. The inductive effect of cyclopropyl is discussed further in Section VI.D but is yet to be fully resolved.

3. Long-lived carbocations

The strong π-donor ability of cyclopropyl is further illustrated by the observation of a variety of long-lived ions with constrained geometries. The NMR spectra of ion **96** was interpreted as arising from a rapidly equilibrating mixture of three degenerate 8,9-dehydro-2-adamantyl cations at $-120°C$[190]. Degenerate rearrangement for **97** was frozen out at $-120\,°C$ but the spectra at $-60\,°C$ were interpreted as arising from two mirror-image equilibrating structures[191].

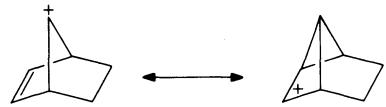


(96)



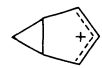
(97)

Long-lived ions derived from the substrates **89** and **90** have also been studied[192] and a topic of particular interest has been the 7-norbornenyl cation (**98a**) which, as shown in **98b**, is a cyclopropylcarbinyl system in which π-donation from one of the ring C–C bonds is effective. These ions may be derived from cyclopropylcarbinyl precursors (**93**)[187, 188] or, more usually, from 7-norbornenyl substrates and have been exhaustively studied, as summarized in some recent reports[193–195].



(98a) **(98b)**

Bicyclo[3.1.0]hexenyl cations (**99**) may be generated from photoisomerism of arenium ions or by ionization or protonation of a number of neutral precursors. The extensive studies of these species have been reviewed[196].

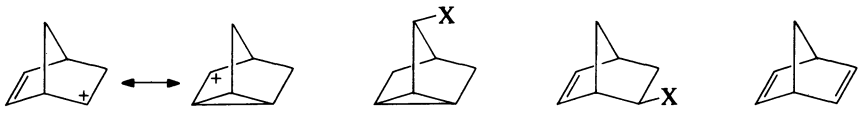


(99)

The possible role of the interconversion shown has also been considered[195].

4. *Nortricyclyl cations*

The 3-nortricyclyl cation **100** can be generated by ionization of either 3-nortricyclyl derivatives (**101**) (Section II.F)[67], 2-norbornen-5-yl substrates (**102**) and by protonation of norbornadienyl derivatives (**103**).

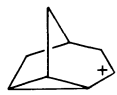


(100a) **(100b)** **(101)** **(102)** **(103)**

Each of these reactions has been studied extensively and each is in principle suitable for generation of **100** for direct observation or examination of its reaction products, but for understanding of the interactions of the geometrically fixed cyclopropylcarbinyl center during solvolysis, **101** is clearly most relevant. As has already been discussed[67] the solvolysis of **101** has been shown to require lessened electron donation by aryl groups at the site of the developing charge, and this ion stability is also reflected in the ^{13}C-NMR shifts of the charged carbons in the product ions[68–70, 195].

Some recent studies of the nature of the intermediates generated in the solvolysis of **102** have appeared, which include the effect of substituents on the rates and stereochemistry of these reactions[197–200, 202].

The long-lived homotricyclyl ion **104** has also been observed under stable ion conditions, and suggested to be undergoing degenerate cyclopropylcarbinyl cation rearrangement[201].

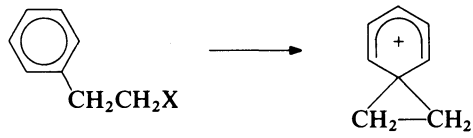


(104)

E. Phenonium Ions

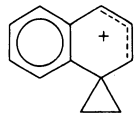
Phenonium ions, of which **105** is the parent species, have long attracted attention, initially concentrated on kinetic and stereochemical evidence for their generation in solvolysis reactions (equation 10), and more recently with direct observation of the ions in solution[203–207]. It has been persuasively argued[205] that these ions are best represented as cyclopropyl-substituted carbocationic systems, with the bisected geometry best suited for π-donation from the cyclopropyl ring.

The naphthalenium (**106**)[206] and anthracenium (**107**)[207] analogs of **106** have also been prepared, and the neutral species **108** was isolated from solvolysis of a *p*-ethylphenolate derivative[208].

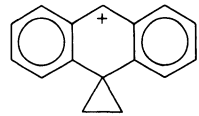


(10)

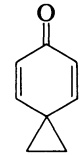
(105)



(106)



(107)



(108)

F. Cyclopropyl-substituted Vinyl Cations

Evidence for the conjugative interaction of cyclopropyl with adjacent vinyl cations comes from a number of sources. Theoretical calculations for a variety of substituted vinyl cations (**109**), including the case where R = *c*-Pr, indicated that substituent effects in **109** were similar to those of the corresponding ethyl cations (**110**)[209]. The rotational barrier calculated for cyclopropylvinyl cation was half that of cyclopropylethyl cation, a result tentatively attributed to conjugation of cyclopropyl with the π-bond of the vinyl cation when the cyclopropyl was twisted perpendicular to the vacant p orbital[209].

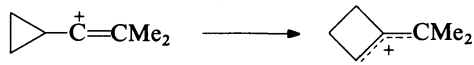
$R\overset{+}{C}=CH_2$ $R\overset{+}{C}HMe$

(**109**) (**110**)

The rates of protonation of substituted alkynes to give **109** were correlated with the corresponding rates for alkenes to give **110** by equation 11, including the case where R = *c*-Pr[210]. The slope of 1.25 was interpreted as showing more efficient conjugation in the developing vinyl cations compared to the ethyl cations because of the shorter bond lengths to the substituent in the former case. Interestingly this effect was not fully realized in the specific case of R = *c*-Pr, as the alkene was more reactive by a factor of 3.

$$\log k_H+(\text{alkyne}) = 1.25 \log k_H+(\text{alkene}) + 1.74 \qquad (11)$$

In an unanticipated result the cation **111** did not react directly with alkenes but instead first underwent the ring expansion reaction shown in equation 12[211], whereas analogous cations $Ar\overset{+}{C}=CMe_2$ gave cycloaddition reactions with alkenes.



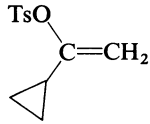
(12)

(**111**)

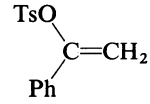
Rearrangement of vinyl cations to place the positive charge adjacent to a cyclopropyl group is more effective than the corresponding reaction to place the charge adjacent to phenyl[212]. Many other aspects of the chemistry of cyclopropylvinyl cations have been summarized in a recent review[213].

The relative reactivity of α-cyclopropyl and α-phenylvinyl tosylates (**112a, b**) may be

calculated to be 200 at 100 °C in 50% MeOH–H_2O by use of the published[214] rate for **112b** under these conditions and that for **112a** with a 2-methyl ring substituent at 100 °C in HOAc[215]. The latter rate is converted to 50% MeOH–H_2O using published Y_{OTs} values[216], an m value of 0.85[217], and the factor 0.10 to correct for the presence of the ring methyl (see Section II.D)[49].

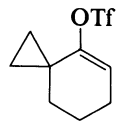


(112a)

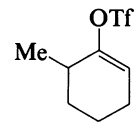


(112b)

The cyclopropylvinyl tosylate **113** interestingly reacted by S–O cleavage in CF_3CH_2OH, although the analog **114** gave a vinyl cation[218]. A possible interpretation of this result is that the σ-withdrawing effect of the cyclopropyl favored S–O cleavage, while a vinyl cation intermediate would have the cyclopropyl perpendicular to the vacant orbital and hence would not provide significant π-donation[218].

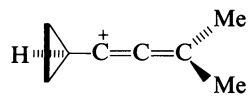


(113)



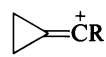
(114)

The cation **115** was directly observed by ^{13}C-NMR and assigned the bisected structure shown[219]. The barrier to rotation was 7.2 kcal mol^{-1}, as compared to 13.7 kcal mol^{-1} for c-Pr$\overset{+}{C}$Me$_2$.



(115)

As discussed in recent reviews[212, 213] the cyclopropylidene cation **116** is significantly stabilized by π-donation from cyclopropyl, as the ring bisects the vacant p orbital in this cation so that π-donation by the ring should be quite efficient.

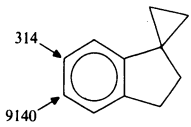


(116)

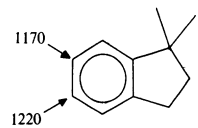
G. Electrophilic Aromatic Substitution of Cyclopropylarenes

These reactions demonstrate not only the strong π-donor ability of cyclopropyl but also the conformational dependence of this effect[15, 30, 33]. Thus the partial rate factors[30] for nitration of **117** and **119** as compared to the models **118** and **120** reveal that the spiro-cyclopropyl in **117**, which is fixed in the bisected conformation, is considerably more

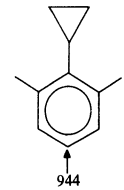
activating to the *p*-position than the isopropyl[15], while the cyclopropyl in **119**, which is twisted into a perpendicular conformation by the *ortho*-methyls, is more electron donating than H[30]. However, as evidenced from σ_p^+ values of -0.21[42] and -0.47 (Table 3) for perpendicular and bisected cyclopropyl, respectively, and σ_m^+ of -0.03 (Table 3), the *m*- and perpendicular *p*-cyclopropyl groups are poorer donors than methyl ($\sigma_m^+ = -0.13$, $\sigma_p^+ = -0.31$)[54].



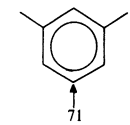
(117)



(118)

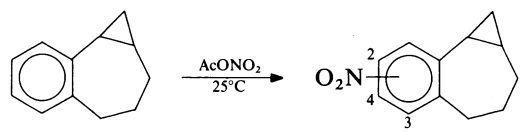


(119)

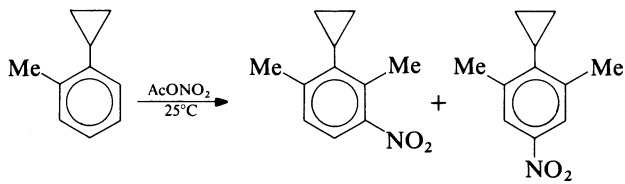


(120)

The nitration results in equations 13 and 14[14,15] were interpreted[7] as showing that 'cyclopropane is a meta director in electrophilic substitution'. Evidently in these systems with the cyclopropane twisted out of the desirable bisected conformation the alkyl group has a stronger directing effect than cyclopropyl and substitution occurs predominantly *o*, *p* to these groups, but this does not indicate an actual *m*-directing influence of cyclopropyl.



2 > 3 > 4 (13)



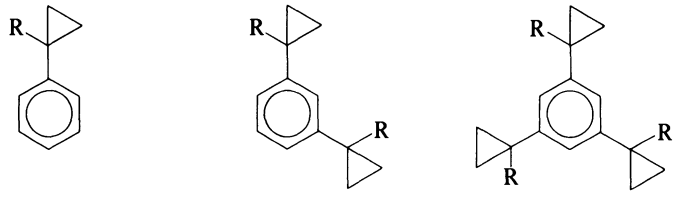
85% 15% (14)

The effect of the *o*-*c*-Pr group in electrophilic aromatic substitution is anomalous[35]. Thus in nitration high *o*, *p*-product ratios were obtained (2.0–4.7), whereas in halogenation the ratios are much lower. It was found in aromatic detritiation, a reaction suggested to be free of steric effects[35], that the ratio of partial rate factors for f_p/f_o for cyclopropyl was 9, and this was interpreted that the high fraction of *o*-nitration was a peculiarity of this particular reaction and not a general effect of the cyclopropyl group[35].

These data also permitted calculation of a σ^+ value for *o*-cyclopropyl of -0.365[35]. This value was judged to be of somewhat smaller magnitude than might have been expected from a comparison of *ortho*-substituent constants for other alkyl groups, and this was tentatively suggested to be due to a steric inhibition of the cyclopropyl group attaining the bisected conformation.

The bromination of the cyclopropylbenzenes **121**, **122** and **123** (R = H) was more facile in every case than for the 1-methylcyclopropyl analogs (R = Me) with substitution

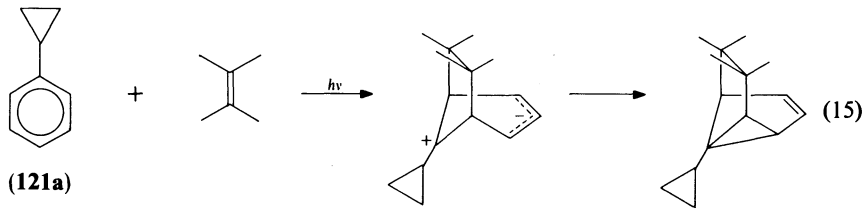
occurring only *para* to the substituent in **121**[220]. This result was interpreted in terms of a late and highly selective transition state for bromination, with a lower reactivity for the 1-methylcyclopropyl compounds due to steric hindrance to adopting the bisected conformation. In nitration there was little difference in the reactivity of cyclopropylbenzenes compared to the corresponding 1-methylcyclopropyl derivatives, a result attributed to the early transition state giving a lack of selectivity. The preference for *o*-nitration in **121** was proposed to be due to preassociation of the attacking NO_2^+ near the cyclopropyl group[220].



(121) **(122)** **(123)**

a: R=H **b**: R=Me

The photocycloaddition of alkenes to cyclopropylbenzene (**121a**) was proposed to involve a dipolar intermediate with the developing positive charge stabilized by the cyclopropyl (equation 15)[221].

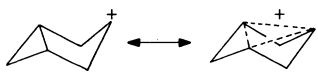


(121a) (15)

H. Homoconjugated Cyclopropyl Cations

The interaction of cyclopropyl groups with cationic centers to which they are not directly attached has been thoroughly reviewed by Haywood-Farmer in 1974[222] and so this work will not be discussed in detail here, with the exception of noting a few recent further studies in this area.

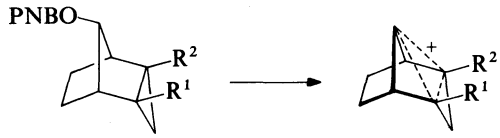
There have been several recent tests of the importance of the delocalization shown in **124**. The long-lived ion of this structure has been observed by NMR, and the spectra interpreted as supporting the symmetrical trishomocyclopropenium structure[193, 223]. However, a variety of methyl and phenyl analogs were all proposed to exist as either allylic or cyclopropylcarbinyl structures[193]. The ^{13}C-chemical shifts and ^{13}C–^1H coupling constants for the two distinguishable types of carbons in **124b** are shown.



(124a) **(124b)**

4.9 (J = 195.4)
17.6 (J = 168.4)

The use of methyl groups in place of hydrogen at R^1 and R^2 in **125** gave evidence that supported symmetrical delocalization as shown in **126** for the product ion[224]. This

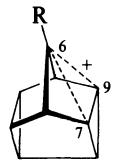


(16)

(125) (126)

interpretation was based primarily on product studies and not the kinetics, which were inconclusive.

The ion **127** has been generated by solvolysis[225-227] and studied as a long-lived ion[228,229]. These experiments have been consistently interpreted in terms of delocalization as shown. The studies have included the 'tool of electron demand' for **127** (R = Ar)[226-228] and the isotopic perturbation technique for R = D[229]. In this latter experiment the 67.9 MHz ^{13}C-NMR spectrum of the long-lived ion showed that the signal for C(6, 7, 9) was shifted less than 0.1 ppm compared to the undeuterated ion, consistent with the delocalized structure and inconsistent with the much larger effect expected for equilibrating ions[229].



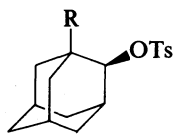
(127)

The solvolysis of β-cyclopropylethyl tosylate (**128**, R = *c*-Pr) has been reinvestigated and the rate relative to **128** (R = *i*-Pr) at 75°C is 0.92, 0.96, 1.1, and 3.4 in EtOH, HOAc, HCO_2H and CF_3CH_2OH, respectively[230]. These low ratios and product studies using deuterium-labeled substrates indicated that solvent displacement predominated over cyclopropyl participation[230], but there was a relative enhancement of the latter for 1-methylcyclopropyl[231]. Optically active *c*-$PrCH_2CHDOTs$ underwent solvolysis with 17–18% retention, consistent with contribution from the k_Δ route[232].

RCH_2CH_2OTs

(128)

The effect of a 1-cyclopropyl substituent on the rate of solvolysis of 2-adamantyl tosylates (**129**) has been compared to a variety of other 1-substituents[233]. These rate effects were attributed to electronic substituent effects on formation of a bridged ion, but steric effects are probably also involved and a detailed interpretation of the conjugative effect of cyclopropyl is not straightforward.



(129)

R	H	Me	*i*-Pr	*t*-Bu	*c*-Pr	Ph
k_{rel}	1	21.4	149	2640	43.3	7.5

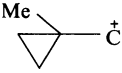
I. Thermochemistry of Cyclopropyl-substituted Cations

The influence of cyclopropyl on the gas phase stability of carbocations as measured by ion cyclotron resonance is shown in Table 14, along with data for some reference compounds. The results are given as gas phase basicities, GB, and proton affinities, PA, defined as $\Delta G°$ and $\Delta H°$, respectively, for dissociation of the protonated molecule, as in equation 17[234]. In addition hydride affinities $D(BH^+H^-)$ for some cations defined as $-\Delta H°$ for equation 18 are included[235]. For the gas phase basicities and proton affinities the products B are alkenes, amines, nitriles or carbonyl compounds, and thus for these values the stability of the cation is compared to a derivative where the substituent is conjugated with a carbon–carbon or carbon–oxygen double bond, or a nitrogen lone pair, whereas for hydride affinities the products are saturated.

$$BH^+ \rightarrow B + H^+ \qquad \Delta G° = GB \qquad \Delta H° = PA \tag{17}$$

$$BH^+ + H^- \rightarrow BH_2 \qquad -\Delta H° = D(BH^+H^-) \tag{18}$$

TABLE 14. Gas phase basicities, proton affinities and hydride affinities for cations

BH^+	GB[a]	PA[a]	$D_{BH^+H^-}$[b]	SE[c]
$MeCH_2^+$		163.5	272.5	
Me_2CH^+	176.5	184.9	249.7	22.8
Me_3C^+	188.3	196.9	234.8	14.9
c-PrC$^+$HMe	190.8	198.8	233.3	39.2
c-PrC$^+$Me$_2$	200.9	209.3	220.8	28.9
PhC$^+$HMe	194.4	202.4	229.2	43.3
PhC$^+$Me$_2$	199.8	208.2	221.3	28.4
	198	206		
c-Pr$_2$C$^+$Me	209.5	217.5		
Ph$_2$C$^+$Me	204.3	212.3		
c-PrN$^+$H$_3$	206.6	215.0		
PhN$^+$H$_3$	203.1	211.5		
MeN$^+$H$_3$	205.7	214.1		
i-PrN$^+$H$_3$	211.0	219.4		
MeC≡N$^+$H	183.1	190.9		
i-PrC≡N$^+$H	188.3	196.1		
c-PrC≡N$^+$H	189.3	197.1		

[a] GB and PA (kcal mol^{-1}) defined by equation 17 and taken from Ref. 234 relative to GB and PA values for NH_3 of 196.4 and 205.0 kcal mol^{-1}, respectively. Values of the PA of the first seven entries were also reported in Ref. 235 based on a PA of NH_3 of 202.3 kcal mol^{-1}, and if these are increased by 2.7 kcal mol^{-1} to the same reference value for NH_3 as used in Ref. 234 the comparative values are in good agreement.

[b] kcal mol^{-1} (equation 18), Ref. 235.

[c] Difference in $D_{BH^+H^-}$ for the hydrogen-substituted analog and the indicated cation.

The cation stabilization afforded by different groups can be usefully analyzed by comparing the hydride or proton affinities of the substituted cation with a derivative where the substituent is hydrogen, and these stabilization energy (SE) values are given in Table 14. As can be seen, these SE values for cyclopropyl are significantly larger than those

for methyl, whereas in comparison to phenyl the cyclopropyl SE is 4.1 kcal mol^{-1} less for the secondary system and 0.5 kcal mol^{-1} more for the tertiary system. These relative values are discussed further in Section V.J.

It has also been found that there is a linear correlation between $\Delta G°$ values for protonation of hydrocarbon alkenes to the carbocations in the gas phase with those in solution, with slope equal to 1.2[236]. This correlation included *c*-$Pr_2C{=}CH_2$ and $Ph_2C{=}CH_2$ and led to the conclusion that the protonation of the former was more favorable by 4 kcal mol^{-1} than the latter in either the gas phase or aqueous solution. However, it was further suggested that the constancy of this number derived from an enhanced stabilization of each cation in the gas phase, which arose predominantly by π-donation for *c*-Pr, and polarization for Ph[236]. Thus the correlation of solution and gas phase results is coincidental.

The protonation of cyclopropylamine is quoted to be more favorable than that of aniline by 3.1 and 6.1 kcal mol^{-1} in the gas phase and aqueous solution respectively[237]. The decreased basicity of aniline in water was attributed to attenuation of the stabilization by polarization of the anilinium ion in aqueous solution, because of hydrogen bonding of the NH_3^+ groups[237]. The generally lower basicity of aniline was attributed to conjugative stabilization of the free base, which is more effective than that for *c*-Pr, but in the gas phase this is partially offset by the greater polarizability of phenyl[235].

As seen in Table 14 gas phase protonation of cyclopropylamine is 0.9 kcal mol^{-1} more favorable than for methylamine but 4.4 kcal mol^{-1} less favorable than for isopropylamine. A possible explanation of the latter large difference is stabilization of cyclopropylamine by the conjugative interaction shown in Figure 3, Section III.D, and inductive destabilization of the cation by cyclopropyl.

The gas phase protonation of cyclopropyl cyanide is 1.0 kcal mol^{-1} more favorable than isopropyl cyanide (Table 14) and much more favorable than for the methyl or ethyl derivatives[234, 238]. Thus, even though there may be ground-state conjugative stabilization of cyano by cyclopropyl (Section IV.F) the net effect favors protonation of this derivative, in contrast to the situation for the amines, where π-donation does not occur in the protonated forms.

TABLE 15. Comparative gas phase ($GB_{(g)}$) and solution phase ($SB_{(aq)}$) basicities and proton affinities (PA) in kcal mol^{-1} of protonated carbonyl compounds[a]

BH^+	$GB_{(g)}$	$PA_{(g)}$	$SB_{(aq)}$	$PA_{(aq)}$
i-$PrC^+(Me)OH$	193.3	201.1	255.9	275.0
$(i\text{-Pr})_2C^+OH$	196.8	204.2	255.0	274.6
c-$PrC^+(Me)OH$	197.1	204.9	256.7	277.9
$(c\text{-Pr})_2C^+OH$	203.6	211.0	257.5	277.0
$PhC^+(Me)OH$	198.1	205.9	254.9	271.7
Ph_2C^+OH	203.9	211.3	254.0	273.2
i-$PrC^+(OMe)OH$	193.6	201.4	254.5	272.4
c-$PrC^+(OMe)OH$	194.9	202.7	254.7	275.2
$PhC^+(OMe)OH$	195.8	203.6	251.8	262.9

[a] All values derived from Ref. 237, GB and PA defined by equation 17. $GB_{(g)}$ and $PA_{(g)}$ calculated from $\Delta G°$ and $\Delta H°$ values in Ref. 237 by the relations $GB_{(g)} = -\Delta G°_{(g)} + 196.4$, $PA_{(g)} = -\Delta H°_{(g)} + 205.0$ where 196.4 and 205.0 are the GB and PA of NH_3 (kcal mol^{-1}) respectively, from Ref. 234. $SB_{(aq)}$ and $PA_{(aq)}$ calculated from $\Delta G°_{(aq)}$ and $\Delta H°_{(aq)}$, values in Ref. 237 by the relations $SB_{(aq)} = -\Delta G°_{(aq)} + 273.4$ and $PA_{(aq)} = -\Delta H°_{(aq)} + 289.0$ where 273.4 and 289.0 are the sum of 196.4 + 77 and 205.0 + 84 kcal mol^{-1}, respectively, and 77 and 84 are $-\Delta G°$ and $-\Delta H°$ for transfer of NH_4^+ from the gas phase to aqueous solution (kcal mol^{-1}) given in Ref. 237.

The gas phase basicity (GB) values in Table 15 for ketones and esters show that cyclopropyl consistently favors protonation relative to isopropyl, although the difference is only 1.3 kcal mol^{-1} for the esters. Phenyl is slightly more stabilizing than cyclopropyl in each case. In solution the phenyl-substituted compounds in Table 15 are consistently the least basic and cyclopropyl the most basic. The low basicity of the phenyl derivatives in dilute acid has been ascribed to the poor hydrogen bonding to the protonated aryl carbonyl[237].

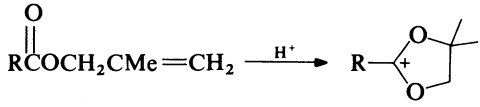
Solution phase heats of reaction ΔH_r for conversion of carbinols to cations in SO_2ClF according to equation 19 have been measured for several cyclopropyl carbinols, and are given in Table 16 with data for suitable reference compounds for comparison[239]. As can be seen ionization of c-Pr_3COH is 10.2 kcal mol^{-1} more exothermic than for Ph_3COH, which is in turn 13.5 kcal mol^{-1} more exothermic than Me_3COH. However, for the carbinols Ph_2CROH the order is Ph > c-Pr > Me.

$$ROH + H^+ \rightleftharpoons R^+ + H_2O \tag{19}$$

TABLE 16. Solution phase heats of conversion of carbinols to cations (equation 19)

ROH	Me_3COH	$PhMe_2COH$	Ph_3COH	Ph_2MeCOH	c-$PrPh_2COH$	c-Pr_3COH
ΔH_r (kcal mol^{-1})	−35.5	−40.3	−49.0	−37.5	−44.3	−59.2

Two thermodynamic measures of heats of protonation of carbonyl compounds in solution to give substituted cyclopropylcarbinyl cations have been reported. Protonation and cyclization of allyl esters gave dioxolenium ions (**130**) (equation 20), but ΔH_{R^+} was the same within the precision of the measurements for R = Me, Et, i-Pr, t-Bu and c-Pr[240]. Thus in these experiments no extra stabilizing ability of cyclopropyl relative to other alkyl groups was detected, but in these ions most of the charge would be delocalized onto oxygen. Since the relative ground state energies are not known, an accurate assessment of the stabilizing ability of cyclopropyl is not obtained[240].



(20)

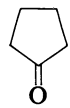
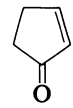
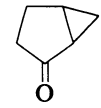
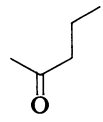
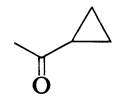
(130)

The heats of protonation of the ketones **131–135** (Table 17) indicate that the vinyl and cyclopropyl groups both give a nearly 5 kcal mol^{-1} more favorable heat of reaction, and consideration of ground state energies probably would make the difference even greater[241].

J. The Relative Conjugating Ability of c-Pr, Ph and Me

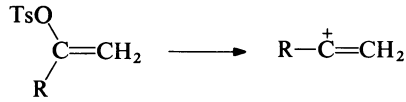
The comparison of the ability of cyclopropyl, phenyl and methyl to conjugate with a positively charged center has been a classic problem in physical organic chemistry[239]. The debate on this topic took on a new lease of life with the conclusion by Olah and coworkers 'that the relative effectiveness of the phenyl, methyl and cyclopropyl groups to delocalize charge shows the order Ph > c-Pr > Me'[242]. This conclusion was based on the analysis of a large body of ^{13}C-chemical shifts of the center of positive charge in carbocations of

TABLE 17. Heats of protonation of ketones

			
ΔH (kcal mol^{-1})	−18.4	−23.3	−23.1
	(131)	**(132)**	**(133)**
			
ΔH (kcal mol^{-1})	−18.8	−22.5	
	(134)	**(135)**	

which those for the series $R\overset{+}{C}Me_2$ of 254.4 (Ph), 280.6 (*c*-Pr) and 329.2 (Me) were most important. However cyclopropyl was recognized to be more effective than phenyl in enhancing solvolysis[242].

The relative rates of solvolysis for $RCMe_2OPNB$ of 1 (Me), Ph (969), and *c*-Pr (503×10^3) was taken as evidence by Brown and Peters[243] that the net electron-donating ability of these groups increased in this order. Other examples of the *c*-Pr > Ph order of substituent effects on solvolysis rates are found in systems **112** and **136** which give k(*c*-Pr)/k(Ph) rate ratios of 200 in the former (Section V.F), and 34 in the latter (equations 21, 22)[244].



(21)

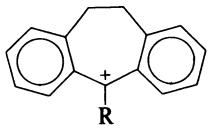
(112)

(22)

(136)

Other related systems in which the relative effect of these groups on ^{13}C-NMR chemical shifts were considered include the dibenzodihydro- and dibenzotropylium ions **137** and **138**, respectively[245] and alkenyl cations **139**[246]. Interestingly, in **139** it was concluded that *c*-Pr equalled or exceeded Ph in its ability to delocalize charge[246].

The effect of the groups R on the rotational barriers to interconversion of the ions **140a** and **140b** (equation 23) was studied, and the results were interpreted that the charge delocalizing ability was *c*-Pr > Ph > Me[247].



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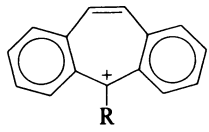

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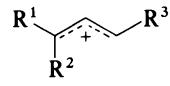

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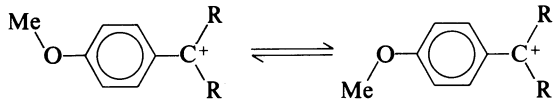


(140a) (140b) (23)

The fact that hydride rearrangement of **141** to give the substituted vinyl cation (equation 24) was evidently more facile for *c*-Pr than for Ph was taken as evidence for the order *c*-Pr > Ph > Me for the stabilizing ability[212]. Cyclopropyl was also better than phenyl in accelerating protonation of alkynes, but only by a factor of 3 (Section V.F)[210].

$$RCH{=}\overset{+}{C}Me \rightarrow R\overset{+}{C}{=}CHMe \qquad (24)$$

(**141**)

The comparative ability of *c*-Pr, Ph and Me in promoting electrophilic additions to alkenes is discussed in Section VI.D.

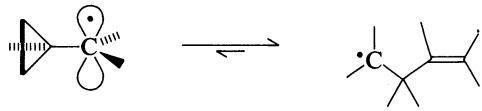
Calculations using STO-3G and 4-31G basis sets led to the conclusions that the stabilizing effect was Ph > *c*-Pr > Me in both trisubstituted and vinyl cations[209]. For the thermochemical data discussed in Section V.I the relative stabilizing ability of *c*-Pr and Ph was variable, but there was a tendency for Ph to be a relatively better substituent in less stable carbocations, but to be less efficient in solution. Theoretical explanations have been advanced for the former behavior[248,249], in that the stabilizing ability of the polarizable Ph is enhanced in situations of high electron demand, such as the gas phase or less substituted carbocations. In solution the relative stabilizing ability of phenyl is diminished due to poorer hydrogen bonding to the phenyl-substituted cations and a lower demand for electron donation[239].

Consideration of these results led Arnett and Hofelich[239] to 'emphasize the utter failure of any regular order for the effects of these groups. Clearly, inversions representing large energy changes are produced by changing the type of cation to which the group is attached, the process being observed, and the medium surrounding the ion. The effects are large enough to provide a delightful challenge to theoretical chemistry.'

VI. CYCLOPROPYL-SUBSTITUTED REACTIVE INTERMEDIATES

A. Cyclopropylcarbinyl Radicals

Cyclopropylcarbinyl radical is indicated by its ESR spectrum to prefer the bisected conformation **142**[250–252], and while this species is stable below −140°C, rearrangement occurs above this temperature and at −100°C only the allylcarbinyl radical (**143**) is observed (equation 25). The bisected form (**142**) is calculated using the STO-3G basis set to be only 1.4 kcal mol^{-1} more stable than the perpendicular form[253], whereas ring-opening has been calculated to be exothermic by STO-3G and MINDO-3 methods[254–257] and by experiment **143** is favored by 5.1 kcal mol^{-1}[258]. The ring-opening of equation 25 has a



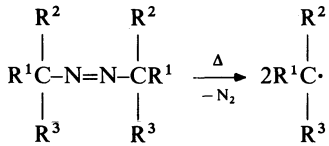
(142) (143) (25)

rate constant of $1.3 \times 10^8\ s^{-1}$ at 25°C[252] and is the fastest of a group of free radical rearrangements collected to serve as free radical clocks[259]. The reverse reaction was found by deuterium labeling to have a rate constant of 4.9×10^3 at 25°C[259, 260]. There have been many studies of the stereochemistry of reaction 25 for substituted cyclopropylcarbinyl radicals and these have been reviewed[259, 261a].

Theoretical studies of reaction 25 and a portion of the di-π-methane rearrangement (equation 25a) suggested these processes have similar energetics even though the details of the transformations were found to be different[261b].

 (25a)

Evidence for cyclopropyl stabilization of free radicals is seen in the relative rates of thermal dissociation of diazenes (**144**) according to equation 26 (Table 18)[262]. The accelerating effect of *c*-Pr is shown not to be due primarily to steric factors by the low rates for the *i*-Pr derivatives included. The fact that **144e** on irradiation at 0°C gave only (*c*-Pr)$_3$CC-(Pr-*c*)$_3$ (**145**) and no ring-opened products was argued to show that concerted ring-cleavage of the cyclopropyl rings on thermolysis of **144** does not contribute to the observed rates[262].

 (26)

(144)

TABLE 18. Reactivities for cleavage of diazenes **144** at 135°C[262].

Compound	R^1	R^2	R^3	k_{rel}
a	Me	Me	Me	1.0
b	Me	Me	*c*-Pr	26.8
c	Me	*c*-Pr	*c*-Pr	362
d	*i*-Pr	*c*-Pr	*c*-Pr	286
e	*c*-Pr	*c*-Pr	*c*-Pr	2540
f	*i*-Pr	*i*-Pr	*i*-Pr	206[a]

[a] k_{rel} at 180°C, Ref. 263.

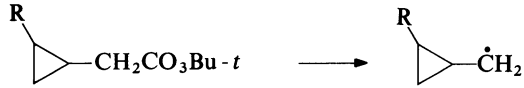
The thermal dissociation of **145** (equation 27) gave a $\Delta G^{\ddagger}$ of 41.5 kcal mol^{-1}[262] as compared to a value of 43.1 kcal mol^{-1} for Et_3CCEt_3[263]. It is clear that steric factors contributed significantly to the reactivity of both these compounds and the relative

contribution of cyclopropyl conjugative interactions in dissociation of **145** has not been disentangled.

$$(c\text{-Pr})_3\text{CC-(Pr-}c)_3 \xrightarrow{\Delta} 2(c\text{-Pr})_3\text{C}\cdot \qquad (27)$$

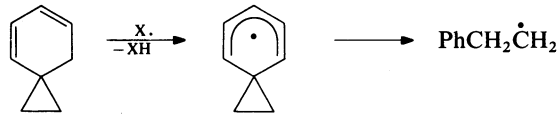
(145)

Studies of ring-substituted cyclopropyl peracetates did not reveal any significant rate enhancement attributable to cyclopropyl conjugation (equation 28)[264].

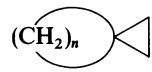


(28)

Spiro[2.5]octadienyl radical (**146**), the radical analog of the phenonium ion (**105**), is a very short-lived species but was detected by its visible absorption and fluorescence on generation by radical abstraction from **147** prior to facile ring-opening to **148** (equation 29)[265]. There appeared to be a modest (two-fold) acceleration compared to 1,3- or 1,4-cyclohexadiene in the rate of abstraction from **147**, and this was attributed to stabilization by a favorable interaction between cyclopropyl and the adjacent semioccupied orbital in **146**[265]. Kinetic acceleration was also proposed to occur in hydrogen atom abstraction from spiro[2.*n*]alkanes (**149**)[266].

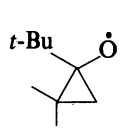


(147) **(146)** **(148)** (29)



(149)

A variety of other radical species (**150–152**) substituted with cyclopropyl groups were postulated to occur as transition states or intermediates in some radical rearrangements[267]. However, any conjugative stabilization present in these intermediates was insufficient to give them appreciable lifetimes.



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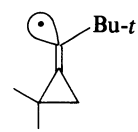
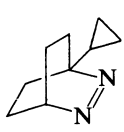


(151)

(152)

The reactions of a variety of cyclopropyl-substituted 2,3-diazabicyclo[2.2.2]oct-2-enes such as **153–155** have been studied and compiled[268–270]. It was proposed[269] that these all underwent photochemical loss of nitrogen with formation of singlet 1,4-diradicaloid species, which gave mixtures of ring-closed and ring-opened products (equation 30).



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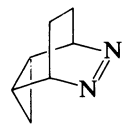

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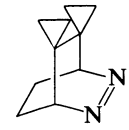

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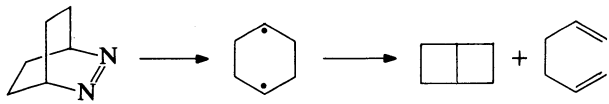
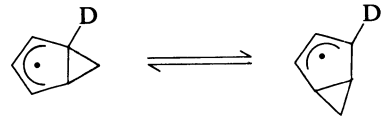


(30)

Sigmatropic rearrangement of deuterium-labeled bicyclo[3.1.0]hexenyl radicals occur below $-60°C$ (equation 31) and are faster than ring-opening[271]. Lifetimes for ring-opening of some cyclopropyl-substituted radical anions (**156**)[272] have been studied, as well as the ESR spectra of *p*-cyclopropylnitrobenzene radical anion (**157**)[273].



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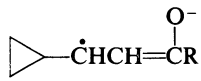

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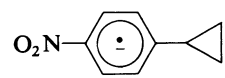
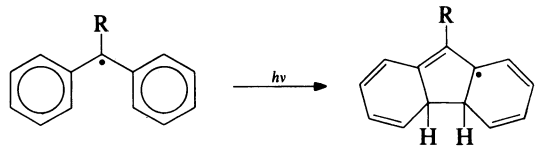


(157)

The heat of formation of the cyclopropyl radical has been measured, and a value of 13 kcal mol^{-1} was assigned to the additional strain that results in cyclopropane if a π-bond center is incorporated in the ring. This strain was suggested to be the reason π-interaction of the cyclopropane ring is relatively ineffective in the stabilization of **142**[274].

The photochemistry of the radicals **158** was studied and proposed to involve a monophotonic excitation to the first excited doublet and then cyclization to a fluorenyl-type radical. However, there was no significant difference for R = Me, *c*-Pr or Ph, and the photoreactivity compared to some less crowded benzyl radicals was proposed to arise from the degree of twisting of the aryl groups (equation 32)[275].

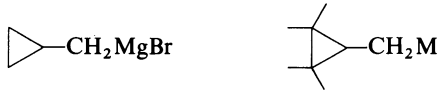


(32)

(**158**), R = *c*-Pr, Me, Ph

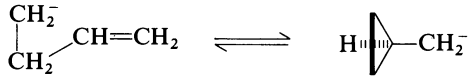
B. Cyclopropylcarbinyl Anions

Cyclopropylmethyl Grignard reagents have a tendency to undergo ring-opening to allylcarbinyl species but by the use of Mg atoms deposited at low temperature a high yield of **159** was obtained and trapped by carbonation[276]. The tetramethyl analog **160** has been found to be the only detectable isomer present at room temperature, and can be formed from either the cyclopropylcarbinyl or the allylcarbinyl chlorides[277]. The X-ray structure of the Li derivative **160b** showed the CH_2 group was pyramidal, with a gauche arrangement of the CH_2 relative to the ring[278]. Steric interactions would be expected to play an important role in determining this conformation.



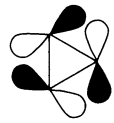
(**159**) (**160a**), M = MgCl; (**160b**), M = Li

A simple HMO calculation for the cyclization of the allylcarbinyl to the cyclopropylcarbinyl anion (**161**) has appeared (equation 33)[279] and, based on proton affinities, **161** was calculated to be 10 kcal mol^{-1} more stable than ethyl anion (SCF double-zeta basis)[99] and 14.3 kcal mol^{-1} more stable than *i*-$PrCH_2^-$ (STO-3G)[83]. The bisected geometry was predicted to be most stable, with electron donation from the filled p orbital at C(4) to the unoccupied Walsh $4a_2'$ MO (**162**) at C(1). Inductive electron withdrawal by cyclopropyl would also stabilize this anion.



(33)

(**161**)



(**162**)

Studies of the base-catalyzed H–D exchange of benzylcyclopropane (**163**)[280] and cyclopropylacetophenone (**164**)[281a] and analogous compounds did not reveal any large kinetic effects due to cyclopropyl stabilization of the resulting anions.

(**163**) (**164**)

The kinetics of proton exchange and pK_a measurements for substituted nitromethanes in two solvent systems showed consistently that cyclopropyl was more effective than isopropyl in promoting proton removal (Table 19)[282]. However, the acid-strengthening

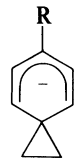
TABLE 19. pK_a values of some nitromethanes[282]

	pK_a (50% MeOH–H_2O)	pK_a (DMSO)	k_{rel}[a]
c-$PrCH_2NO_2$	9.41	16.53	10.6
i-$PrCH_2NO_2$	10.38	17.1	3.3
c-$PrCHMeNO_2$	8.73		0.22
i-$PrCHMeNO_2$	9.73		0.095
c-Pr_2CHNO_2	10.64		0.079
i-Pr_2CHNO_2	11.0		6.1×10^{-4}
c-$PrNO_2$	> 18	26.9	0.002
c-$HxNO_2$	10.07	17.9	0.28

[a] Relative rates of proton removal (50% MeOH–H_2O).

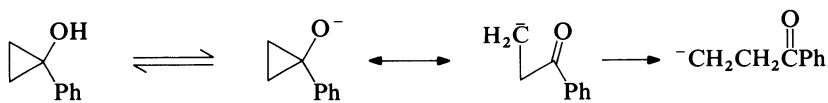
effect of c-Pr was much smaller than the effect of phenyl or vinyl, and was interpreted as a small inductive effect, with little or no conjugative effect. The comparison of c-$PrCH_2NO_2$ to c-Pr_2CHNO_2 shows the latter is a weaker acid, and this was attributed to some unfavorable interaction between the two c-Pr groups. For comparison the effect of a second i-Pr group is not as acid weakening, so that (c-Pr)$_2$CHNO$_2$ is only 0.36 pK_a units stronger an acid than i-Pr_2CHNO_2[282].

Substituted derivatives of the spiro anion **165**, analogous to the phenonium ion, have been suggested as long-lived intermediates in solution on the basis of trapping experiments[283], although the parent species R = H could not be intercepted in this way.



(165)

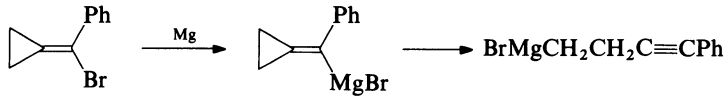
The anion of cyclopropanol was predicted on the basis of theoretical calculations to be stabilized by electron donation to the ring[99] and a pK_a of 14.2 for **166** was estimated based on the rates of base-catalyzed cleavage of the alcohol (equation 34)[284a]. The pK_a of 2-phenyl-2-propanol was estimated to be 16.1 and the significantly greater acidity of **166** was ascribed to a major contribution of a resonance structure (**167**), which resembles the ring-cleavage product from this alkoxide. The rates of cleavage of cyclopropanols under basic conditions are 10^5–10^9 faster than those of the corresponding cyclobutanols[284b].



(34)

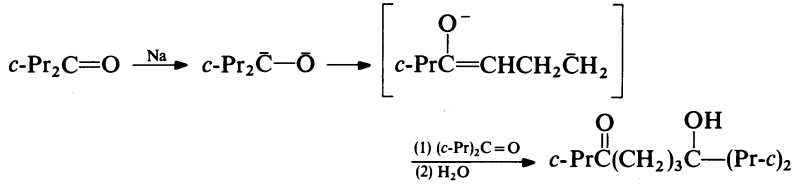
(166) **(167)**

Reaction of the bromide **168** with Mg was proposed to involve the Grignard reagent (**169**) which underwent ring opening (equation 35)[285]. The radical derived from bromine loss from **168** was also proposed to form and undergo ring-opening.



(168) (169) (35)

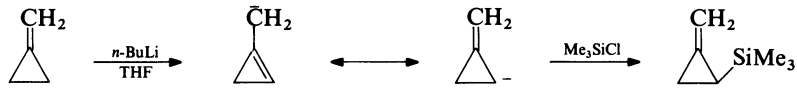
Formation of **170** from the reaction of dicyclopropyl ketone with Na was attributed to formation of a dianion which rearranged and added to another molecule of ketone (equation 36)[286]. An alternative route would involve cleavage of a radical anion and then reduction.



(36)

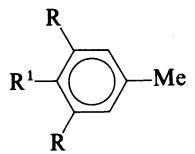
(170)

1-Cyclopropenylcarbinyl anions have been generated, including the parent species (**171**) as well as substituted derivatives[287]. Reaction with carbon or silicon electrophiles favored substitution on the ring[287].



(171)

Rates of hydrogen isotope exchange by *t*-BuOK in DMSO as noted below indicated that there was no detectable conformational effect on the anion stabilizing effect of *c*-Pr compared to *i*-Pr[281b].

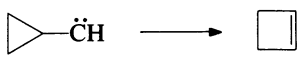


k_{rel}	R = H	R = Me
R^1 = *c*-Pr/*i*-Pr	2.3	2.8[a]

[a] Calculated using a derived rate for the case where R^1 = *c*-Pr.

C. Cyclopropylcarbenes

Carbenes are well recognized as cyclopropane precursors, but cyclopropylcarbenes are more elusive because of their propensity in the singlet state to undergo ring-enlargement to cyclobutene (equation 37)[288, 289], although triplets as in the case of equation 38 are long-lived enough to trap alkenes[289a].



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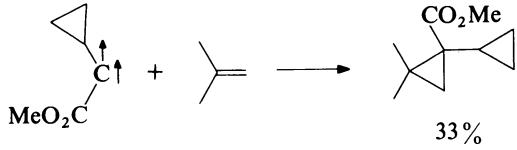
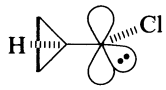
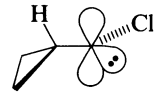


(38)

However, singlet cyclopropylchlorocarbene (**172**) is trapped in 78% yield by tetramethylethylene[289b]. Relative reactivity studies of **172** with a variety of alkenes suggested, however, that it was not as selective as predicted based on the polar character of the *c*-Pr and Cl substituents[36]. It was proposed that this lack of selectivity arose from the need for a conformational change from a preferred bisected ground state **172a** to a perpendicular array **172b** for addition to an alkene because of steric interactions in the transition state for addition of **172a** to alkenes[36].



(172a)



(172b)

Calculations at the STO-3G level confirmed that **172a** was more stable than **172b**, by 9.5 kcal mol^{-1} and also indicated that the perpendicular form **172b** would be significantly less selective[36].

An efficient route to dicyclopropylcarbene (**173**) has also been reported[290]. In contrast to other singlet carbenes the reaction of **173** with chloroform proceeded by C–H insertion, and this result was rationalized in terms of a non-synchronous concerted process in which the transition state had significant character of the dicyclopropylmethyl cation (equation 39)[290].

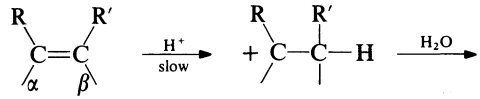
$$(c\text{-Pr})_2\text{C:} + \text{HCCl}_3 \longrightarrow [(c\text{-Pr})_2\overset{+}{\text{C}}\text{H}\cdot\bar{\text{C}}\text{Cl}_3]^{\ddagger} \longrightarrow (c\text{-Pr})_2\text{CHCCl}_3 \qquad (39)$$

(173)

D. Cyclopropyl Substituent Effects on Additions to Alkenes

The unique substituent properties of cyclopropyl make it a useful probe for organic reaction mechanisms. The strong π-donor ability of cyclopropyl is manifested by the σ_p^+ and σ^{C+} constants of -0.48 and -1.33 (Table 3), and there is evidence that cyclopropyl can act as a π-acceptor as well (Section III.A)[82,83]. However, when direct conjugation is not possible the donor ability of cyclopropyl is greatly reduced, as evidenced by the σ_m^+ constant of -0.04 (Table 3). As discussed in Section V.D.2 the inductive effect of cyclopropyl is not well understood, but cyclopropyl is clearly a poorer σ-donor than saturated alkyl groups, while the relative position of cyclopropyl and hydrogen is ambiguous.

The properties of cyclopropyl make it an effective aid in the study of transition states to detect whether or not there is significant positive charge development that can interact with a π-donor. It was proposed[291] that in cases where the transition states have the character of open carbocations that large (ca. 10^3) *c*-Pr/Ph rate ratios should accrue, as demonstrated for the comparison of acid-catalyzed hydration of *c*-$PrCH{=}CH_2$ to $PhCH{=}CH_2$ (equation 40). A number of other examples of this behavior have now been demonstrated as collated in Table 20[292–298].



(40)

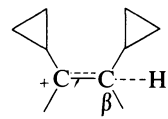
TABLE 20. Comparative reactivity of cyclopropyl-, phenyl- and methyl-substituted alkenes ($R^1R^2C{=}CH_2$) in acid-catalyzed hydrations

	k_H^+ ($M^{-1}s^{-1}$) (H_2O, 25°C)			k(c-Pr)/k(Ph)	k(c-Pr)/k(Me)	
R^1	R^2 = c-Pr	R^2 = Ph	R^2 = Me			Ref.
H	2.54×10^{-4}	3.72×10^{-7}	2.38×10^{-9}	680	1×10^5	291–293
c-Pr	10.6	1.30×10^{-2}	0.200	815	53	292
Me	0.200	9.67×10^{-5}	3.71×10^{-3}	2100	54	292
Ph	1.30×10^{-2}	—	9.67×10^{-5}	—	134	292
OMe	7.46×10^3	5.45×10^1	2.26×10^2	140	33	294
OAc	3.59×10^{-3}	9.9×10^{-6}	5×10^{-5}	360	72	295
OPO_3Et_2	1.04×10^{-5}	1.11×10^{-5}	1.72×10^{-5}	0.9	0.6	295
$CH{=}CH_2$	1.22×10^{-2}	—	3.19×10^{-5}	—	380	296
$OSiMe_2Bu\text{-}t$[a]	132	0.919	21.6	144	6.1	297

[a] 50% acetonitrile–H_2O.

There are six examples of k(c-Pr)/k(Ph) rate ratios ranging between 140 and 2100 in Table 20. There is one value near unity, for substituted vinyl phosphates, but the value for the phosphate was considered anomalous by the original investigators[295] and remains so. For alkene protonations the net rate effects reflect the difference in conjugation of the substituent with the alkene reactant and the product ion, but the conclusion appears inescapable that cyclopropyl is significantly better than phenyl in conjugating with the developing ion. The general tendency for methyl to accelerate protonation more than phenyl probably arises partly from greater ground state stabilization by phenyl.

The effect of β-cyclopropyl groups on hydration according to equation 40 was demonstrated to be decelerating relative to hydrogen or methyl, as shown by the data in Table 21. This effect was interpreted in terms of the transition state **174**, in which the rate effect of β-c-Pr was correlated with a term proportional to the σ_m^+ parameter of cyclopropyl (−0.04) and another term proportional to the estimated stabilizing effect of cyclopropyl on a double bond (4.4 kcal mol^{-1})[298].

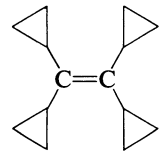


(174)

TABLE 21. Relative rates of acid-catalyzed hydration of cyclopropylalkenes[298]

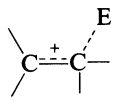
c-PrCH=CH-Pr-c (Z)	0.08	$c\text{-Pr}_2C{=}CH_2$	4×10^4
c-PrCH=CH-Pr-c (E)	0.03	$c\text{-PrCMe}{=}CH_2$	800
c-PrCH=CHMe (Z)	0.2	$c\text{-PrCH}{=}CH_2$	1.0
c-PrCH=CHMe (E)	0.1	$c\text{-Pr}_2C{=}C\text{-(Pr-}c)_2$	0.08[299]

The rate of reaction of tetracyclopropylethylene (**175**) in aqueous H_2SO_4 as measured by disappearance of the UV absorption was correlated by the equation $\log k = -0.98H_0 - 6.98$ ($r = 0.985$), with $k_H+/k_D+ = 2.0$, and **175** reacted at rates very similar to *Z*-1,2-dicyclopropylethylene at the same acidities[299]. Thus this compound is much less reactive than 1,1-dicyclopropylethylene[299].

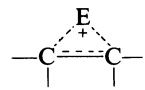


(**175**)

The 10^6 greater rate of hydration of (*c*-Pr)$_2$C=CH$_2$ relative to the isomeric *E*-*c*-PrCH=CH–Pr-*c* is a powerful argument that protonation of alkenes occurs via the open transition state **176a**, as opposed to the proton-bridged intermediate **176b**. There is overwhelming evidence against any general role for **177a**[300], although there are persistent proposals[301, 302] and rebuttals[303, 304] of the occurrence of **177a** in protonations and other reactions.



(**176**)



(**177**) **a**: E = H **b**: E = ArS

In contrast to the large span in reactivities observed for the cyclopropylalkenes in acid-catalyzed hydration the total range for addition of *p*-ClC$_6$H$_4$SCl is only 75 (Table 22)[305]. This latter reaction is known to occur through rate-limiting formation of a bridged thiiranium ion (**177b**)[306a] and the relatively small difference of the rates of the 1,1- and 1,2-dicyclopropyl isomers, and the similarity in substituent effects of methyl and cyclopropyl groups, are all in accord with this proposal. The regiochemistry of these additions has also been examined[306b].

The use of cyclopropyl substituent effects was applied as a diagnostic tool for the elucidation of the mechanism of two much more ambiguous reactions, namely methoxymercuration[307] and bromination[308]. In the former reaction *c*-PrCH=CH$_2$ is 410 times as reactive as 1-hexene, and (*c*-Pr)$_2$C=CH$_2$ and *c*-PrCMe=CH$_2$ are even more reactive. In contrast the isomeric *c*-PrCH=CHMe were even less reactive than 1-hexene. These rate

TABLE 22. Relative rates of electrophilic additions to cyclopropylalkenes

Alkenes	H_3O^+	ArSCl	Hg^{2+}
c-PrCH=CH$_2$	1.0	1.0	1.0
c-PrCH=CH–Pr-*c*(*Z*)	0.08	6.0	
c-PrCH=CH–Pr-*c* (*E*)	0.03	3.1	
c-PrCH=CHMe (*Z*)	0.2	6.6	0.002
c-PrCH=CHMe (*E*)	0.1	4.9	0.0008
c-PrCMe=CH$_2$	800	11	5.1
(*c*-Pr)$_2$C=CH$_2$	4×10^4	24	6.6
n-BuCH=CH$_2$		0.3	0.002

effects (Table 22) were interpreted as showing highly unsymmetrical transition states resembling **176** for these reactions, although other alkenes, such as $CH_2{=}CH_2$, evidently react through bridged transition states[307].

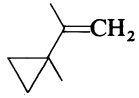
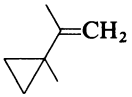
In bromination cyclopropylalkenes are extremely reactive, and *c*-PrCH=CH_2 was estimated to be at least 10^3 times more reactive than *n*-BuCH=CH_2[291]. An analysis of the bromination reactivity of a large number of alkenes led to the conclusion that while most reacted through bridged bromonium ions that *c*-PrCH=CH_2 proceeded through an open ion[308].

The reaction of singlet oxygen with cyclopropylethylenes followed by reduction with Ph_3P gives allylic alcohols and interestingly these include significant amounts of the isomers with double bonds exocyclic to the cyclopropane rings despite the strain induced in this way (equation 41)[309–311]. The relative reactivities of cyclopropyltrimethylethylene equalled that of tetramethylethylene[309]. The results favored a transition state without positive charge localization next to cyclopropyl.

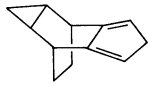
(41)

The relative rates of dichlorocarbene addition to cyclopropylalkenes showed some significant differences (Table 23) that were attributed to the combined influence of steric and electronic factors[312]. It was concluded that unique effects due to the cyclopropyl groups did not occur in this concerted cycloaddition[312].

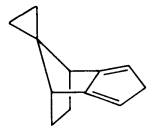
TABLE 23. Relative rates of CCl_2 addition to alkenes[312]

Alkene	k_{rel}	Alkene	k_{rel}
$(c\text{-Pr})_2C{=}CHMe$	2035	Cyclohexene	200
c-PrCMe=CH_2	1415	$CH_2{=}CHCH{=}CH_2$	140
c-$Pr_2C{=}CH$-Pr-*c*	970	*c*-PrCH=CH_2	100
$Me_2C{=}CH_2$	950		76
c-$Pr_2C{=}CH_2$	910	*i*-PrCH=CH_2	12
$CH_2{=}C(Me)CH{=}CH_2$	830	*i*-$Pr_2C{=}CH_2$	9
	744	*t*-BuCH=CH_2	1

The effects of remote cyclopropane rings on the stereoselectivity in [4+2]-cycloadditions of the dienes **178** and **179** and some analogs have been studied[313, 314].



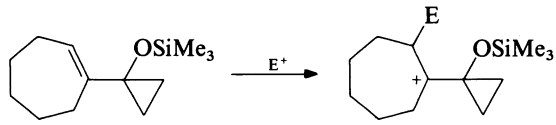
(178)



(179)

Some large effects attributed to interaction with the cyclopropyl groups were observed[313, 314].

The cation stabilizing ability of the 1-(trimethylsilyloxy)-cyclopropyl group has been utilized to activate alkenes to attack by relatively weak electrophiles as illustrated in equation 42[315].

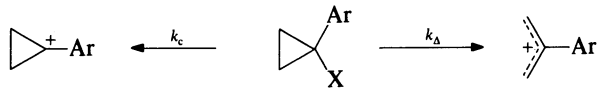


(42)

E. Reactions on the Cyclopropyl Ring

1. Cyclopropyl cations

Species with positive or negative charge or a free radical site on the cyclopropyl ring are formally outside the scope of this survey but a few recent investigations deserve mention. These species are highly strained if an sp^2 carbon is incorporated in the ring, and the strain in these species is often relieved by ring-opening, as was observed in the solvolysis of a series of 1-arylcyclopropyl derivatives (**180**) (equation 43)[316–318].



(43)

(**180**)

It was found that for the very strong electron-donor aryl groups *p*-dimethylaminophenyl and 5′-coumaranyl that no ring-opening occurred during solvolysis and the only products observed were unrearranged alcohols[318]. For less powerful donors ring-opening occurred, and amounted to 95% of the product when aryl was *p*-tolyl. A rate-product correlation dissected the solvolysis into two processes, namely k_c giving the unrearranged cation, and the accelerated ring-opening path k_Δ. The former had $\rho^+ = -7.07$, while the latter gave $\rho^+ = -2.47$[318].

These results permitted the completion of a correlation of $\log k$ for 1-*p*-anisyl-1-cycloalkyl *p*-nitrobenzoates versus ρ^+ for the cycloalkyls with 3 through 8 ring carbons. Also a rate could be calculated for the unobserved k_c process for 1-cyclopropyl tosylate, and the actual observed rate with ring-opening was found to be accelerated by 10^{12} [318].

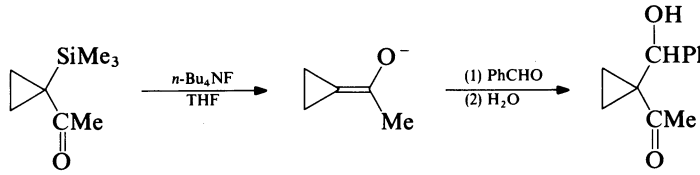
Cyclopropyl cations substituted with strong donor groups such as NHMe (**181a**) and OMe (**181b**) have been directly observed by ICR[319] and NMR[320], respectively. A theoretical comparison of 1-substituted cyclopropyl cations and the isomeric allyl cations has also been presented[321a].

R = NHMe (**181a**)
R = OMe (**181b**)

The S_N2 reaction of cyclopropyl triflate and the stereoisomeric 2-methylcyclopropyl triflates have been observed to occur with clean inversion[321b].

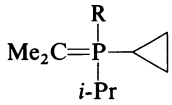
2. Cyclopropyl anions

Cyclopropyl anions that are not conjugated to π-acceptor groups are pyramidal and are resistant to ring-opening, but cyclopropyl ketones are difficult to enolize. However, the corresponding enolates can be generated as useful synthetic intermediates by the route of equation 44[322]. The configurational stability of a variety of cyclopropyllithiums and other anionic species have been elucidated in an extended study by Walborsky and coworkers[323]. Theoretical studies of 1-substituted cyclopropyl anions have also appeared[324–326] and gas and solution phase acidities measured[234, 327, 328].

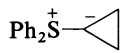


(44)

Proton removal from mixed cyclopropylisopropylphosphonium salts to form phosphoranes gave only the products **182** resulting from proton removal from the isopropyl group[329]. However, sulfur ylids such as **183** may be prepared[330] and have found wide application in synthesis[315]. Equilibrium acidities of cyclopropanes substituted with a variety of sulfonyl-type substituents have also been measured[331].



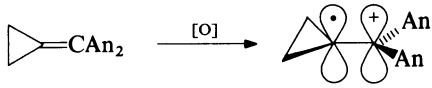
(182) (R = *i*-Pr or *c*-Pr)



(183)

3. Cyclopropyl radicals

Cyclopropyl radicals are also stable to ring-opening and a number of these species have been generated and observed by ESR[332, 333]. An unusual example is the radical cation **184**, generated by oxidation as shown in equation 45[334a]. The conformation shown was assigned to **184**, in which the cyclopropyl ring delocalizes neither charge nor spin[334a].



(45)

(184)

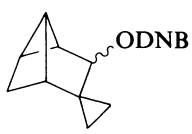
An = *p*-Anisyl

Rate constants for hydrogen atom abstraction by cyclopropyl radical from tri-*n*-butylstannane and germane have been measured, and relative reactivities for a series of hydrocarbon radicals are Ph (350), *c*-Pr (50), Me (7.0), and *t*-Bu (1.0)[334b]. A review of the properties of cyclopropyl radicals with particular emphasis on stereochemistry and substituent effects has appeared[334c].

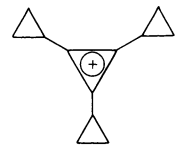
F. Other Cyclopropylcarbinyl Cation Systems

In addition to the ions related to **89** and **90** and the ion $(c\text{-Pr})_3\overset{+}{C}$, the subject of a classic study[335], there are several other cations substituted with more than one cyclopropyl worthy of mention.

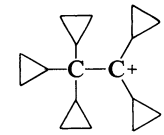
The solvolysis of system **185** has been examined[336] and the tricyclopropylcyclopropenium ion (**186**)[337, 338] and the pentacyclopropylethyl cation (**187**)[339] generated as long-lived species. The high stability of **186** was shown by the pK_{R^+} value and the UV spectrum[337, 338]. The cyclopropyl groups in **187** underwent rapid equilibration and were not resolved in the NMR[339].



(185)



(186)

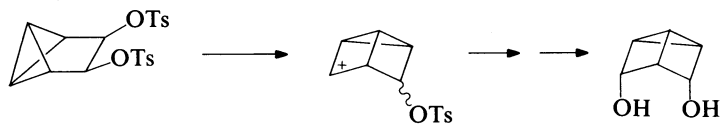


(187)

Just as in β-cyclopropylethyl systems (**128**, R = *c*-Pr)[230–232] cyclopropyl has been found to be an inefficient migrating group to positive oxygen in the Criegee rearrangement[340].

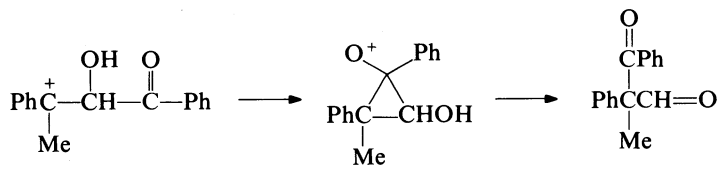
The rate of nucleophilic addition to cyclopropyl-substituted cations is little affected by the cyclopropyl[341]. Thus there was little difference in the rate of reaction of $Ph\overset{+}{C}HR$ and $Ph\overset{+}{C}R_2$ (R = Ph or *c*-Pr) with NH_3, *n*-Pr_3N, and *n*-Bu_3N in methylene chloride solvent except for Ph_3C^+, which was less reactive by factors of 10–20. Steric factors were evidently responsible for the latter effect[341].

The preparative solvolysis of **188** in aqueous acetone gave **189** (equation 46)[342]. This reaction was interpreted as involving initial solvolysis with cleavage of one cyclopropyl ring, followed by hydration and a second solvolysis.



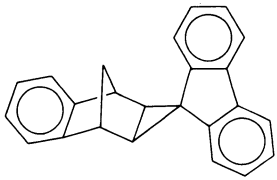
(188) (189) (46)

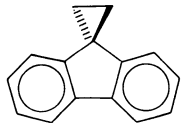
The cation **190** was proposed as a transition state in the rearrangement of equation 47, with stabilization by π-donation from cyclopropyl[343]. Similar behavior was observed in geometrically fixed derivatives[344].



(190) (47)

Cyclopropyl substituted cation radicals have been generated by electron transfer from the derivatives below, and showed electron donation by one or two cyclopropane C–C bonds, respectively[345].





VII. CONCLUSION

The use of the cyclopropyl group as a mechanistic tool is finding increasingly more numerous and diversified applications. Many interesting examples have undoubtedly been inadvertently omitted, for which the current author must accept the blame. The support of the Natural Sciences and Engineering Research Council of Canada for our own studies in Toronto is gratefully acknowledged, and thanks are due to Professors H. C. Brown, M. Charton, G. A. Olah and J. D. Roberts for helpful comments.

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CHAPTER 11

Solvolysis of cyclopropyl-substituted derivatives

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I. INTRODUCTION

The topic 'solvolysis of cyclopropyl-substituted derivatives' in its broadest sense should cover all of those reactions of cyclopropane-containing compounds in which some portion of the reaction solvent is incorporated into the product. However, the literature of cyclopropane-containing molecules is extensive, and use of such a broad definition of the term 'solvolysis' in cyclopropane chemistry would encompass too large an area for a single review. Also, it would result in too much overlap with other chapters in this volume, namely Chapters 11 and 12 concerning synthetic uses of and rearrangements involving the cyclopropyl group. Thus, the present review has in general been limited to studies involving the solvolyses of halide, carboxylate ester or sulfonate ester derivatives where kinetic studies have been, or readily could have been carried out. Studies involving primarily acid-catalyzed reactions of alcohols or alkenes, or deaminations of amines, etc., have mostly not been included.

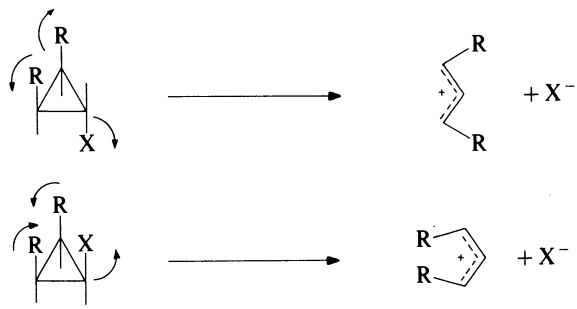
The primary literature surveyed for the present review has consisted mainly of articles published from 1965 to 1984. However, the coverage although comprehensive has not been encyclopedic. Also, in several cases where a certain topic has been covered previously in a detailed review, it is usually simply summarized here with only the literature subsequent to the review being presented in detail.

II. CYCLOPROPYL SYSTEMS

A. Introduction

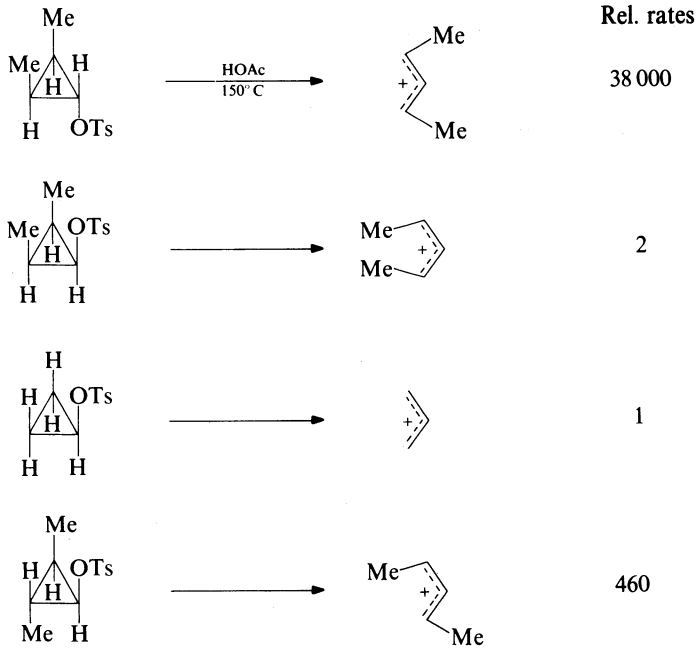
A number of reviews dealing with various aspects of the solvolytic chemistry of systems leading to cyclopropyl carbocations have appeared[1–7]. The most recent of these reviews[7] is found in an earlier volume in this series.

Initial interest in the solvolyses of cyclopropyl derivatives stemmed from the observation that they underwent solvolysis with concerted ring-opening[8], and that the reaction was strongly dependent on the nature and stereochemistry of substituents on the ring[9]. This was explained by Woodward and Hoffmann[10] who predicted from orbital symmetry considerations that the electrocyclic transformation in which a cyclopropyl carbocation is converted to an allyl cation should occur in a disrotatory fashion. Also, the particular disrotatory path a given system will take should be dependent on the stereochemistry of the leaving group. This is illustrated as follows.



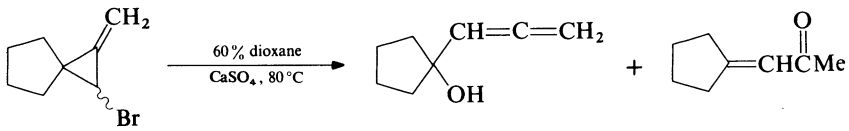
B. Non-ring-fused Systems

Much of the initial work on the solvolyses of non-ring-fused cyclopropyl derivatives was carried out to determine the effects of the nature and stereochemistry of substituents on their rates of reaction and direction of cyclopropyl–allyl ring-opening. The reviews by DePuy[1,9], Schöllkopf[2], Wendisch[4] and especially by Aksenov[6], and coworkers summarize this early work which agreed with the theoretical predictions of Woodward and Hoffmann[10]. Examples of some of the kinetic results are shown in Scheme 1[2,11].



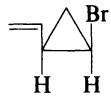
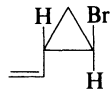
SCHEME 1. The relative rates of acetolysis at 100°C of some cyclopropyl tosylates[2,11]

In more recent work, Léandri and coworkers[12] have solvolysed a series of methylene dialkyl and methylene spiro cyclopropyl bromides as a method for preparing α-allenic tertiary alcohols. An example is shown below in the reaction of **1**. Robertson and



(1) 60%

coworkers[13] have studied the solvolyses of a series of methyl, vinyl and methyl–vinyl substituted cyclopropyl bromides.

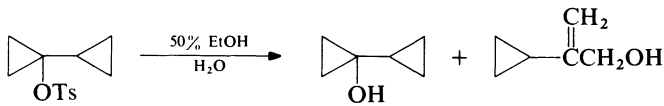
$k_{rel.}$ 1 280 3000

H_2O, 100°C

Various studies have been carried out to determine the effects of changes in α-substituents on the chemistry of cyclopropyl derivatives[14, 15]. An α-phenyl substituent was observed to accelerate the rate of acetolysis of cyclopropyl tosylate by a factor of 10^5. Even though the product was 2-phenylallyl acetate, it was suggested that the high sensitivity of α-arylcyclopropyl tosylates to the introduction of substituents onto the aromatic ring is due to the fact that the activated complex is an aryl-stabilized cyclopropyl cation, not a ring-opened allyl cation species.

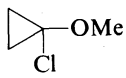
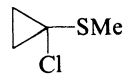
Brown and coworkers[16, 17] have published several papers concerning solvolyses of 1-aryl-1-cyclopropyl 3,5-dinitrobenzoates in 80% aqueous acetone. A plot of log k versus σ^+ revealed, by its non-linearity, a change in mechanism as electron demand at the cationic center increases. The more electron-releasing substituents give more unrearranged cyclopropyl product. Thus the cyclopropanol to allyl alcohol ratios were: *p*-MeO, 87:13; *p*-MeS, 70:30; and *p*-Me, 5:95. Extrapolation of the tertiary data to the parent cyclopropyl system indicates that solvolysis of the latter must be enhanced by concerted ring-opening by a factor of 10^{12}.

The α-cyclopropyl substituent was found[18, 19] to accelerate the rate of hydrolysis of 1-cyclopropylcyclopropyl tosylate (**2**) in 50% aqueous ethanol at 70°C over that of 1-isopropylcyclopropyl tosylate by a factor of about 16000:1. With the 1-cyclopropyl substituent, the non-ring-opened 1-cyclopropyl cyclopropanol was the major product. Also, there was no degenerate rearrangement in the ion.



(**2**) 68% 32%

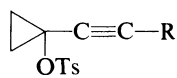
With a 1-phenylthio substituent[20, 21], a dimethyl-substituted chlorocyclopropane gives considerable ring-opening on methanolysis. However, when there are no methyl

(**3**) (**4**)

substituents on the ring as in **3** and **4**, both 1-methoxy and 1-methylthio groups completely suppress ring-opening on methanolysis of cyclopropyl chloride[22].

Several papers concerned with solvolyses of 1-ethynylcyclopropyl tosylates (**5**) have appeared[23–25]. The kinetics and product distribution behaviors were found to be strongly



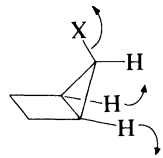
(**5**)

dependent upon the nature of the ethynyl substituent. In 50% aqueous acetone at 70°C the relative rates for R = methyl, phenyl and cyclopropyl were 1:6:133, respectively, with amounts of ring-opening product being 100%, 100% and 10% respectively.

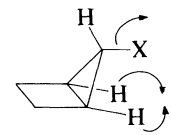
Very recently Creary and McDonald[26] have studied solvent effects on the rates of solvolysis of 1-methylcyclopropyl triflate. Solvents ranging from ethanol to hexafluoroisopropanol and trifluoroacetic acid were examined. This was done as part of a study to define a set of solvent ionizing power values for use in solvolyses of triflates.

C. Ring-fused Bicyclic and Related Monohalide or Sulfonate Ester Systems

Bicyclo[2.1.0]pent-5-yl derivatives are constrained to only one disrotatory mode of ring-opening. Thus, a very large *endo–exo* leaving group rate difference would be expected. An *endo* isomer (**6**) might be predicted to be exceedingly fast owing to relief of ground state



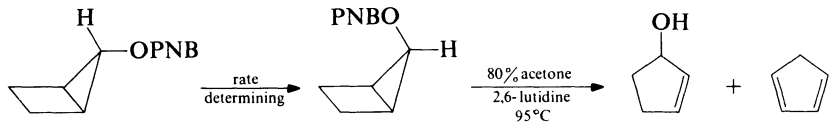
(**6**)



(**7**)

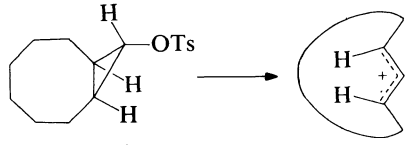
strain on cleavage of the internal cyclopropane bond. On the other hand, an *exo* system (**7**) would be predicted to be essentially unreactive owing to its inability to undergo a concerted, disrotatory ring-opening.

The high reactivity predicted for the *endo*–bicyclo[2.1.0]pent-5-yl system was indeed found[27–29]. However, the *exo-p*-nitrobenzoate or tosylate were also highly reactive, being approximately 10^{18} more reactive than the corresponding *exo*-substituted[3. 1. 0] system. The fact that the reactions were also essentially independent of solvent polarity and that the tosylate was only about six times more reactive than the corresponding *p*-nitrobenzoate (OPNB) led to the explanation that solvolysis of the *exo*-bicyclo[2.1.0]pent-5-yl systems involves an initial rapid isomerization to the very reactive *endo* isomer. This is shown below for hydrolysis of the *exo-p*-nitrobenzoate **7-OPNB**.



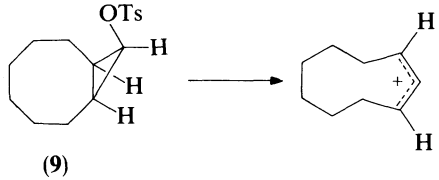
(**7-OPNB**) 62% 38%

With larger bicyclo[n. 1. 0]alkyl cyclopropyl derivatives such as **8** and **9**, their solvolytic behavior follows from that of the simple alkyl–substituted cyclopropyl derivatives[2]. With smaller bicyclo[n.1.0]alkyl cyclopropyl derivatives such as **10** and **11**, however, where a *trans*-allyl cation cannot be accommodated in the ring, the order of reactivity is reversed[2]. In both the [6.1.0] and [3.1.0] examples mentioned above, the rates are given relative to cyclopropyl tosylate. The much higher reactivity of the *endo*-[3.1.0] system (**11**) over the *endo*-[6.1.0] system (**9**) reflects the stability of the almost strain-free cyclohexenyl allylic cation versus the cyclononenyl allylic cation which possesses both torsional and transannular strain.



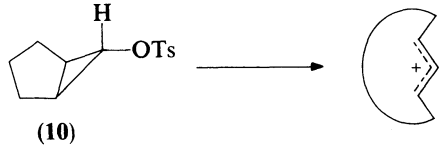
(8)

Rel. rates
HOAc, 100 °C
10000



(9)

3.5



(10)

Rel. rates
HOAc, 100 °C
$\ll 0.01$

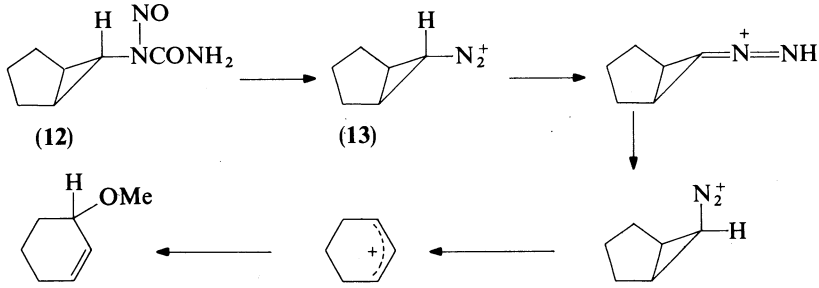
(11)

25000

The behavior in the larger systems in which stereospecific *trans*-double bond formation in rings takes place from solvolysis of *exo*-derivatives has been used successfully for syntheses of *trans*-cyclooctenyl derivatives[30–32], cyclooctadienyl derivatives[33, 34] and cyclotridecenyl derivatives[35].

In other studies, Clark and Smale[36] have investigated the effects of α-phenyl substitution in the solvolyses of *endo*- and *exo*-bicyclo[3.1.0]hexyl through [5.1.0]octyl chlorides. For the *endo* derivatives, where the solvolyses proceed by a favored, concerted disrotatory mechanism in the parent systems, replacement of hydrogen by phenyl gives a relatively small rate enhancement ($k_{Ph}/k_H = 10^2$). On the other hand with the *exo*[3.1.0] and [4.1.0] systems where an initial disrotatory ring-opening is energetically unlikely, the phenyl has a large effect on rate ($k_{Ph}/k_H = 10^6$–10^8) and alters the reaction to a process involving non-concerted ring-opening. However, for the *exo*[5.1.0] system where concerted disrotatory ring-opening can occur, the α-phenyl rate enhancement is again small ($k_{Ph}/k_H = 10^2$).

Kirmse and coworkers[37–41] have made an extensive study of rearrangements in deaminations of bicyclic cyclopropyl derivatives. An important process occurring in the deaminations when the diazonium species are formed by treatment of the corresponding *N*-nitrosoureas (**12**) with aqueous or alcoholic base is the isomerization of *exo*-diazonium ions (**13**) to *endo*-diazonium ions (**14**) prior to loss of nitrogen.



(12) (13) (14)

Many of the more recent studies of solvolyses of bicyclic cyclopropyl derivatives have been done using the triflate (OTf) leaving group. Thus, Creary[42] has published a paper revealing participation by a neighboring double bond and by a neighboring cyclopropyl group in solvolyses of *endo*-tricyclo[3.2.1.$0^{2,4}$]oct-6-ene-*exo*-3-yl triflate (**15**) and *endo*–*exo*-tetracyclo[3.3.1.$0^{2,4}$.$0^{6,8}$]non-*exo*-3-yl triflate (**16**), respectively, shown below.

(15) (16)

Similar studies were also done by Creary[43] on the *exo*-bicyclo[3.1.0]hex-2-en-6-yl and [4.1.0]hept-2-en-7-yl triflates (**17** and **18**).

(17) (18)

Wiering and coworkers[44] reported a study of the solvolysis of 7-*exo*-bicyclo[4.1.0]heptyl triflate in a number of protic solvents at 66°C. They found that the ratios of 7-*exo*-bicyclo[4.1.0]heptyl and 3-cycloheptenyl solvolysis products were similar in the different solvents. This suggests a common intermediate, a partially ring-opened carbenium ion pair, for both products.

Solvolytic studies of the 3-methyl and 3-phenyl substituted *exo*-tricyclo[3.2.1.$0^{2,4}$]oct-*exo*-3-yl derivatives **19** and **20** shown below have revealed[45,46] steric rate enhancements of

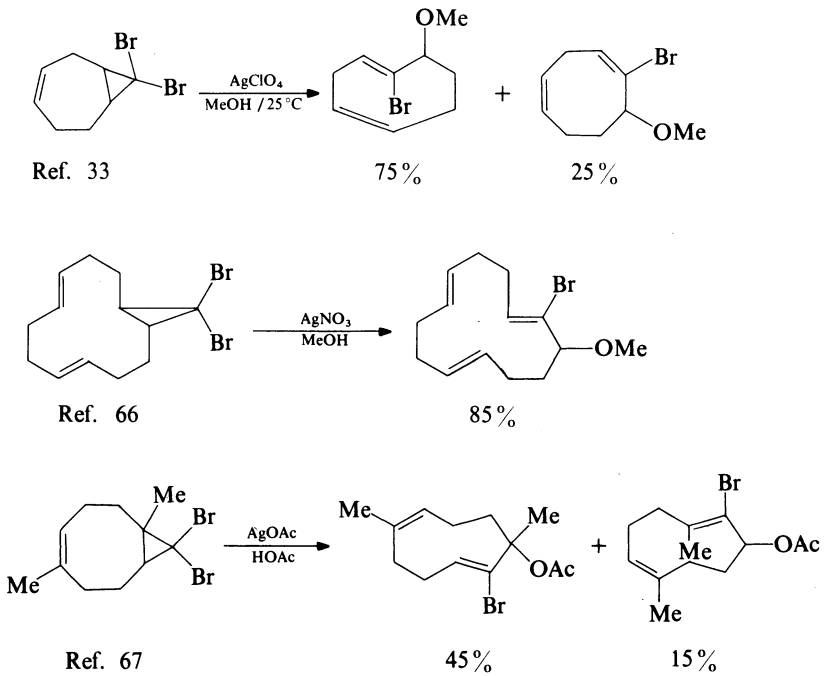
(19) (20) OTFA = $OCOCF_3$

factors of about 10^3 as compared to *non*-norbornyl fused model systems. Conformational factors were suggested to explain the similar magnitudes of the methyl and phenyl steric effects. Very recently, Creary and coworkers[47,48] have reported studies of the response of triflate solvolysis rates to solvent ionizing power in which the tertiary 1-methylcyclopropyl and the *endo*-6-methyl-*exo*-bicyclo[3.1.0]hex-6-yl triflate systems were among those examined. Both systems exhibited good correlations with Creary's Y_{OTf} solvent ionizing parameter based on 7-norbornyl triflate.

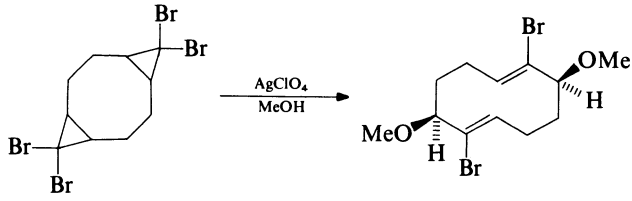
D. Ring-fused Bicyclic and Related Geminal Dihalide Systems

The chemistry of dihalocyclopropanes has been reviewed in several places[3,4,7], the most recent being in 1983 in an earlier volume of this series. The principles involved in explaining the rate and product behaviors observed with the dihalocyclopropanes follow from those described previously for the reactions of monohalo- or sulfonate ester-substituted cyclopropanes and thus will not be repeated here. In most of these studies the solvolytic reactions were silver ion assisted and only qualitative rate data were presented. The major emphasis was on determining by means of product studies whether the *endo* or *exo* halogen was the most reactive in the various systems and thus whether the product was a *cis*- or *trans*-cycloalkene derivative.

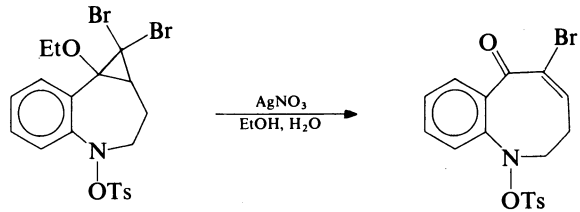
Besides using the reviews[3,4,7] mentioned above, several other articles[49–65] may be consulted as sources for further reference in the field of dihalocyclopropane solvolyses. Most of these papers deal with the chemistry of simple bicyclo[n.1.0]alkyl dihalocyclopropanes. Some examples of more unusual dihalocyclopropane solvolyses which also serve to illustrate the chemistry which can take place are given in Scheme 2[33,66–73].



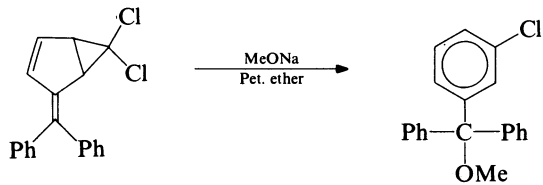
SCHEME 2. Solvolysis products of some unusual dihalocyclopropanes



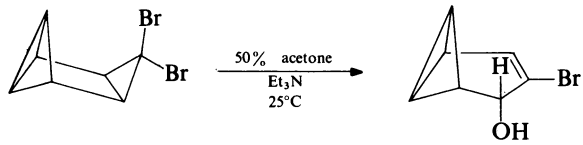
Ref. 68 41%



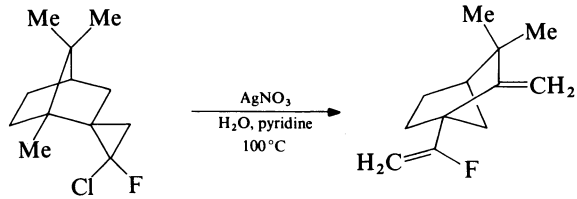
Ref. 69 48%



Ref. 70 70%



Ref. 71 60%



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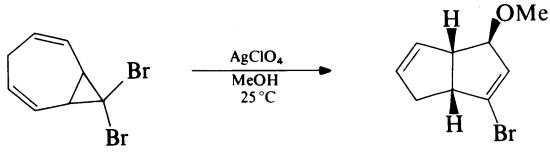
SCHEME 2. *Continued*



Ref. 73 75%

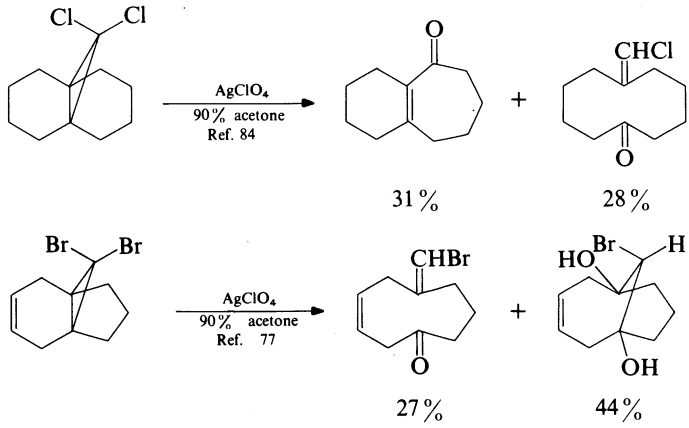
SCHEME 2. *Continued*

E. Mono- and Dihalopropellane Systems

Solvolyses of 10,10-dihalo[4.3.1]- and 11,11-dihalo[4.4.1]propellanes (**21** and **22**), which have been demonstrated to proceed via bridgehead olefin formation[56,74–86], give

(21) **(22)**

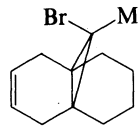
various products depending on the reaction conditions. The rearrangements leading to certain of these products are quite complex.



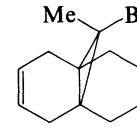
Solvolyses of the epimeric monobromopropellanes **23** and **24** have also been examined by Ledlie and coworkers[82]. However, the products which were originally reported have been reevaluated in a later paper by Warner and coworkers[90].

(23) **(24)**

Ledlie and coworkers[87] have studied the silver ion catalyzed solvolyses of the epimeric double bond containing tertiary propellanes **25** and **26** in methanol. They observed no



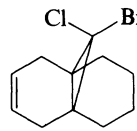
(25)



(26)

rearranged products but instead ones formed largely with retention of configuration via 'bent' cyclopropyl cations. Similar results were found by Kirmse and Engbert[88] in a corresponding deamination. The entire area of bridgehead alkenes was reviewed in 1980 in a report by Shea[89] which included a section on dihalopropellanes.

In a very recent article[90], Warner and coworkers have studied the silver ion promoted hydrolyses of the double-bond containing epimeric bromochloropropellanes **27** and **28**. The product mixtures obtained were exceedingly complex. Thus, space limitations do not



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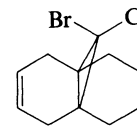


(28)

permit their presentation here. From the results the authors concluded that the epimeric [4.4.1]propell-3-ene halides **27** and **28** afford diastereomeric bridgehead olefins that do not interconvert. Also, the double bond participates in ionization only when it is oriented *anti* to the departing bromine.

More detailed information concerning the reactions of [m.n.1]propellanes is provided in Chapter 20 of this volume.

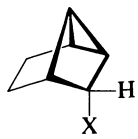
III. CYCLOPROPYLCARBINYL SYSTEMS

A. Introduction

A considerable number of investigations of the solvolytic chemistry of cyclopropylcarbinyl systems have been reported. Consequently, a number of reviews dealing with solvolytic studies involving cyclopropylcarbinyl cation intermediates have appeared[91–98]. The majority of the investigations were carried out as part of mechanistic studies of the nature of and geometric requirements for the stabilization produced at an adjacent cationic center by a cyclopropane substituent. However, as the theoretical and mechanistic aspects of transmission of electronic effects by cyclopropyl substituents have been covered in other chapters in this volume, this review is not organized along mechanistic lines but rather by compound structural types. This should make the review of greater use to the organic chemist for whom cyclopropylcarbinyl–cyclobutyl and cyclopropylcarbinyl–allylcarbinyl cation rearrangements continue to be of considerable synthetic importance.

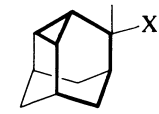
In selecting the various cyclopropylcarbinyl structural types for the review, the main concern was to systematize the available literature in convenient, structurally readily recognizable sections. However, these sections in many cases also correspond to divisions in mechanistic types. Cyclopropylcarbinyl derivatives contained as part structures in

tricyclic or higher systems, where they could be considered simultaneously as representatives of several different bicyclo[n.1.0] systems have been reviewed under the category of the smallest[n.1.0]cyclopropylcarbinyl system present. Several examples are given below.



[2.1.0]

[3.1.0]

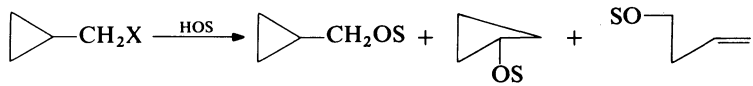


[4.1.0]

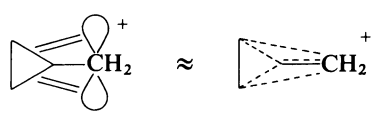
B. Free-rotating Systems

1. Simple

The area of free-rotating cyclopropylcarbinyl systems can be separated into two major categories. The first is where the cyclopropane ring is not contained as part of another ring.

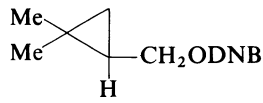


The investigations carried out in this area were done primarily to determine the magnitudes of steric and electronic effects on the solvolytic rates and products of reaction in the cyclopropylcarbinyl cation system. The goal of most of these studies was to learn more about the nature of the charge delocalization in the cyclopropylcarbinyl system and of the stereochemistry of the cyclopropylcarbinyl–cyclobutyl and cyclopropylcarbinyl–allylcarbinyl cation rearrangements. Key papers in these studies were those in 1966 by Schleyer and Van Dine[99], in 1971 by Majerski and Schleyer[100] and in 1974 by Poulter and Spillner[101] which demonstrated that in the simple cyclopropylcarbinyl system

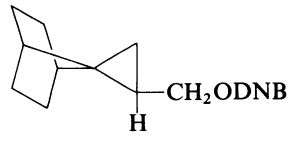


charge delocalization is of the 'bisected' type. These papers are also excellent sources of references for earlier work. Furthermore, the majority of the simple cyclopropylcarbinyl derivative solvolysis studies published prior to 1975 have been adequately summarized, especially in the reviews by Wiberg and coworkers[94] in 1972 and by Brown[98] in 1977. Thus, they will not be covered further here.

Although the previous reviews adequately cover the effects of simple alkyl substituents in cyclopropylcarbinyl systems, they do not mention the case where the cyclopropane ring is part of a spiro system. Thus, Wilcox and Hsu[102] compared the hydrolysis rate in 70% aqueous acetone at 125°C of **30** having a cyclopropylcarbinyl 3,5-dinitrobenzoate attached spiro to the 7-position of norbornane with that of 3,3-dimethylcyclopropylcarbinyl 3,5-dinitrobenzoate (**29**). It was found that with a larger spiro ring as in **30**, the effect on rate was small ($k_{29}/k_{30} = 10$). No products were reported in this study.

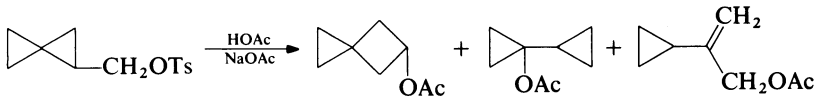


(29)



(30)

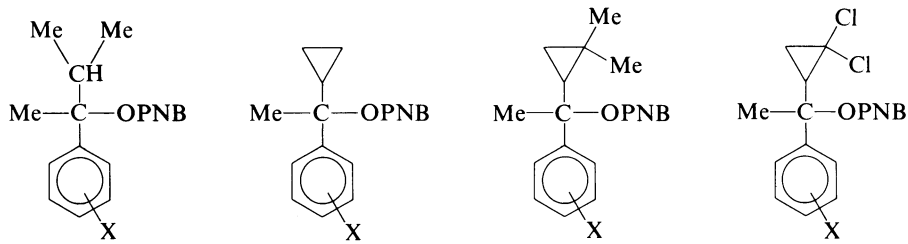
The spiro[2,2]pentylmethyl system (**31**) is of considerable interest. The acetolysis products[103] shown below reveal interesting cyclopropylcarbinyl to cyclobutyl cation and



(31) 48% 11% 23%

cyclopropylcarbinyl to cyclopropylcarbinyl cation rearrangements. These were further investigated using deuterium labeling and methyl-substituent effect probes. Unfortunately, however, no kinetic studies were reported.

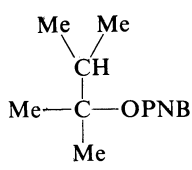
Brown and coworkers[104] have carried out studies in 80% aqueous acetone on a series of 1-cyclopropyl-1-arylethyl *p*-nitrobenzoates (Scheme 3). The relative rate and ρ^+ comparisons reveal that under increasing electron demand the cyclopropyl group is capable of providing σ-electron supply to a better extent than does the isopropyl group, although this is affected strongly by substituents on the cyclopropane ring. From an analysis of the data Brown concluded that the large σ-electron supply provided by the cyclopropane substituent must be classified as σ conjugation, not σ participation.

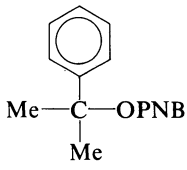


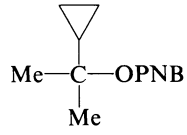
Rel. rates				
X = *p*-MeO	1.0	5.1×10^2	1.7×10^3	3.6
p-H	1.0	2.5×10^4	3.1×10^5	1.9
p-CF_3	1.0	2.9×10^5	1.1×10^7	2.0
ρ^+	−4.76	−2.78	−2.06	−4.99

SCHEME 3. Relative rate and $\rho\sigma^+$ data for hydrolysis of some *p*-nitrobenzoates in 80% aqueous acetone at 25°C[104]

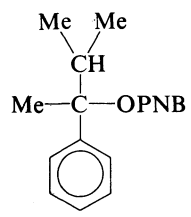
In another report[105], Brown and Peters examined the relative electron-releasing properties of isopropyl, phenyl and cyclopropyl groups to an electron-deficient center. The relative rates given below are for solvolyses in 80% aqueous acetone.

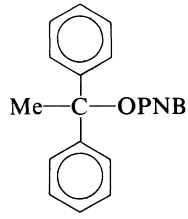


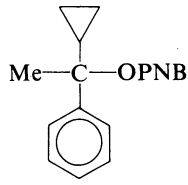




Rel. rates 1.0 3.3×10^2 1.7×10^5

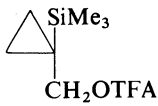


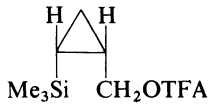


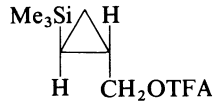


Rel. rates 1.0 72 2.5×10^4

Finally, in a recent paper DeLucca and Paquette[106] have examined the solvolyses of several trimethylsilyl-substituted cyclopropylcarbinyl trifluoroacetates in 2,2,2-trifluoroethanol. This study was initiated to learn of the nature of trimethylsilyl substituent effects in cyclopropylcarbinyl systems. The kinetic results obtained are shown below





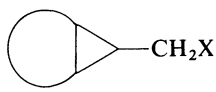


Rel. rates 27 45 25

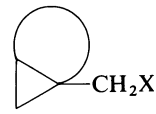
relative to the unsubstituted system. Products were also examined but were found to be complex.

2. *Fused ring*

A second important class of free-rotating cyclopropylcarbinyl systems is that in which the cyclopropane ring is also part of another ring or rings as in **32** and **33**. These studies



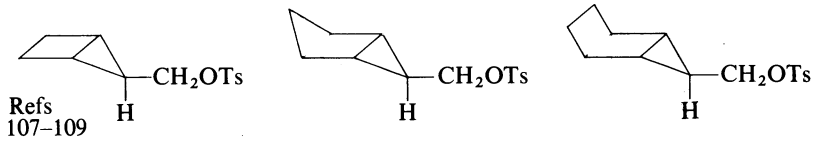
(32)



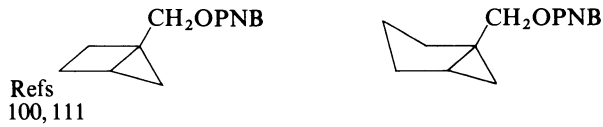
(33)

were carried out in part to learn of the effects of strain in the fused ring on the rates of reaction. However, more important information from the studies was obtained concerning the behavior of cyclopropylcarbinyl cation ring-openings. This area of investigation has been especially well reviewed by Wiberg and coworkers[94] and some typical kinetic data

taken from this review are presented below showing the effects of ring size on reactivity. They are related in general to how much breaking of the bridging bond is taking place in the rate-determining step.

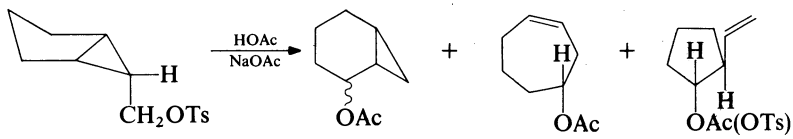


Rel. rates HOAc 1 40 200



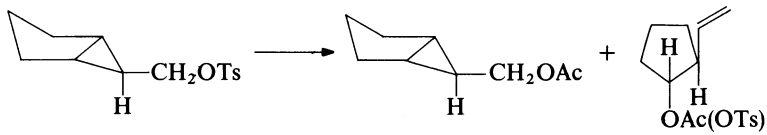
Rel. rates 60% acetone 550 1

Some typical product distributions[108,112] are given in Scheme 4, which illustrates the striking product differences observed with different leaving group–methylene orientations even though the relative rates of reaction are similar. The differences are related to the fact that cyclopropylcarbinyl–cyclopropylcarbinyl cation rearrangement in the *endo* isomer (**34**) can lead to a *cis*-fused cyclopropane ring. However, with the *exo* isomer (**35**) it would have to give a *trans*-fused cyclopropane ring.



(**34**) 59% 19% 20%

Rel. rates = 1.0



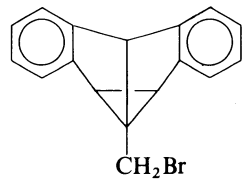
(**35**) 25% 75%

Rel. rates = 1.2

SCHEME 4. The products of acetolysis of several epimeric bicyclo[3.1.0]hex-6-yl methyl tosylates[108–112]

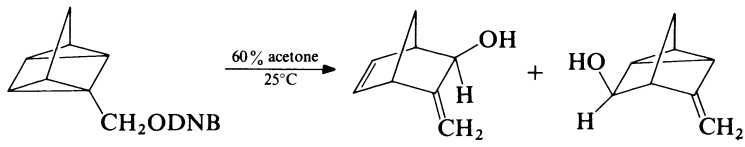
In other work, which was too recent to be reviewed by Wiberg and coworkers[94], Cristol and coworkers[113] studied the silver-assisted acetolysis of the tricyclic cyclopropylcarbinyl

system (**36**) as a possible entry into the 1-dibenzosemibullvalenylcarbinyl cation. The products were mainly those of the three possible cyclopropylcarbinyl–allylcarbinyl cation rearrangements.

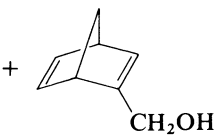


(**36**)

Tabushi and coworkers[114] investigated the solvolysis of 1-quadricyclylcarbinyl 3,5-dinitrobenzoate (ODNB) (**37**) in 60% aqueous acetone at 25°C which gave a mixture



(**37**) 49% 29%

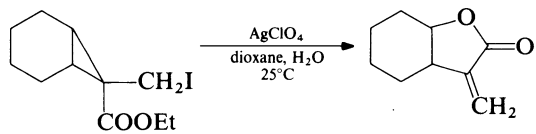


(or ODNB)

22%

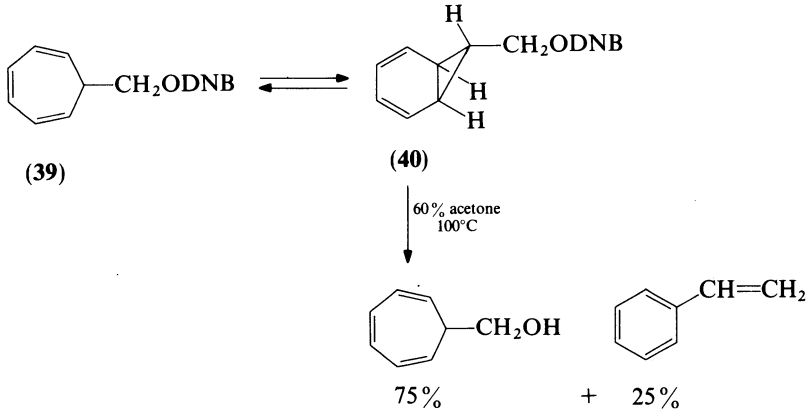
of alcohols and rearranged dinitrobenzoates. The rate of reaction was exceedingly fast being 300 times greater than that for 1-bicyclo[2.1.0]pentylcarbinyl 3,5-dinitrobenzoate. The high reactivity was explained as being due to the extent of about 75% to relief of strain and 25% to a cyclopropyl–cyclopropyl interaction.

An interesting recent case of a solvolytic study of a fused-ring cyclopropylcarbinyl system is that of Hudrlik and coworkers[115] on **38** as part of a synthesis of α-methylene-α-butyrolactones.

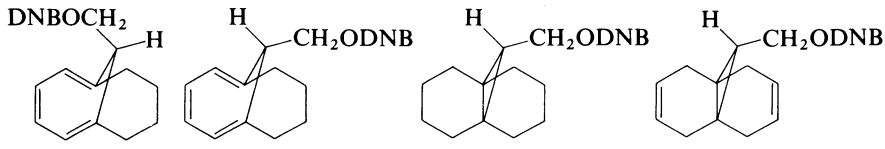


(**38**) 81% yield

In 1967, Sargent and coworkers[116] suggested that the solvolysis of cycloheptatrienylcarbinyl 3,5-dinitrobenzoate (**39**) proceeded via its norcaradienylmethyl valence tautomer (**40**). This work inspired a series of papers reporting investigations designed to confirm the norcaradienyl hypothesis and to determine if the reaction was occurring via the *exo*-methylene dinitrobenzoate isomer as shown above or through the corresponding *endo*

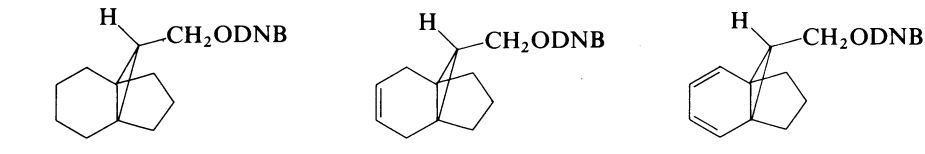


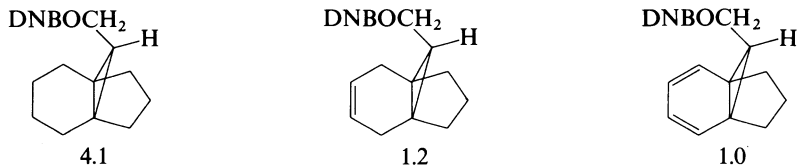
isomer. Some kinetic results provided by Paquette and Thompson[117,119] for solvolysis in 80% aqueous acetone are as follows. Some similar results in 70% aqueous acetone by



Rel. rates 100°C

Warner and Lu[118,120], but in a system where the norcaradienylmethyl valence tautomer is known to predominate are given below. Both studies supported Sargent's[116] norca-



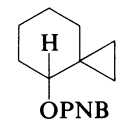


radienylmethyl proposal in that the *anti*-methylene dinitrobenzoate norcaradienyl derivatives were more reactive.

C. Spiro Systems

The solvolytic rates and products for a variety of mono- and dispiro-cyclopropylcarbinyl systems have been investigated. These were done primarily to assess the importance of the geometrical orientation of a cyclopropyl group for maximum electron release to an adjacent developing cationic center.

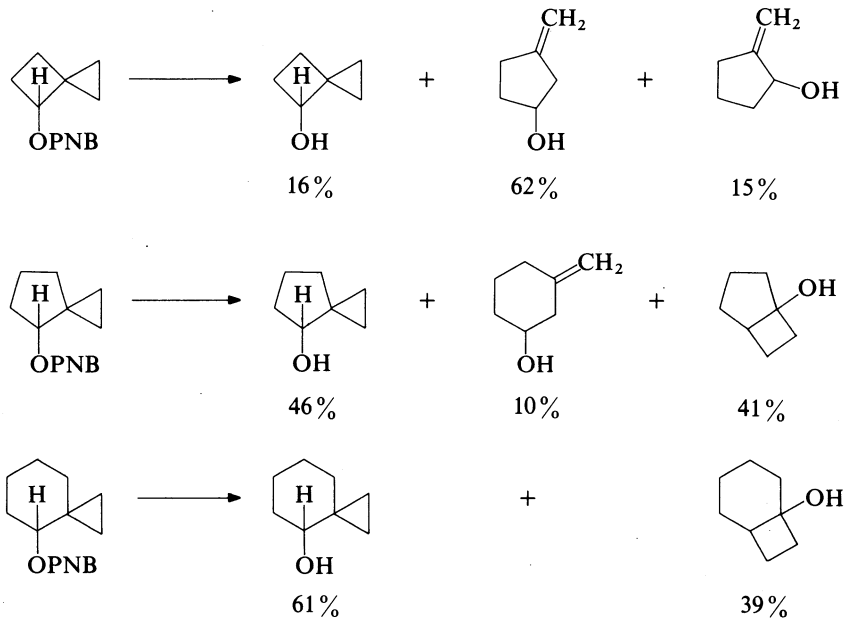
With simple secondary spirocyclopropylcarbinyl systems the cyclopropyl group, owing to its favorable bisected geometry for orbital overlap, generally produces a rate acceleration of about 10^5 over corresponding 2,2-dimethylcycloalkyl systems[121]. The relative rates for the secondary spiro systems shown below[122–124] are for typical



Rel. rates 10^{-3} 1 10^{-1}

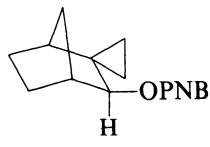
hydroxylic solvents. The geometries of all of the systems are favorable for bisected-type orbital overlap. Thus, the differences in rate simply reflect energy differences related to changes from tetrahedral to trigonal geometry at the reaction site on ionization for the various sized rings.

Hydrolysis products for the spiro[2,3]hexyl to [2,5]octyl systems in 80% aqueous acetone at 100°C are shown in Scheme 5[122–124]. Similar product forming behavior has been observed with other more substituted spiro[2,3]hexyl systems[125].

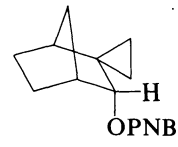


SCHEME 5. Products of hydrolysis of some spiro cyclopropylcarbinyl *p*-nitrobenzoates in 80% aqueous acetone at 100°C[122–124]

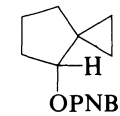
In a study of 3-spirocyclopropyl substituted 2-norbornyl *p*-nitrobenzoates in 70% aqueous acetone, Wilcox and Jesaitis[126] found rate enhancements of about 10^3 and 10^5 for the *exo*- and *endo*-derivatives **41** and **42**, respectively, over the corresponding non-spiro systems. The relative rates of the *exo*- and *endo*-3-spirocyclopropyl norbornyl derivatives



(**41**)



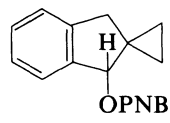
(**42**)



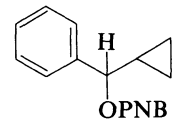
(**43**)

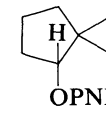
41 and **42** as compared to the simple spiro[2,4]heptyl system **43** in 70% aqueous acetone at 100°C are about 0.05 : 0.02 : 1, respectively, with the lower reactivities reflecting tetrahedral to trigonal energy differences on ionization. In these systems any norbornyl-type rate enhancement is believed to be completely overwhelmed by the cyclopropylcarbinyl interaction. However, the products were largely the *exo*-alcohols with the cyclopropane ring intact.

In a recent study in 80% aqueous acetone[127], a spirocyclopropyl substituted indan-1-yl *p*-nitrobenzoate (**44**) was observed to have unusually high reactivity indicating stabilization both by the cyclopropane and benzene rings. A Hammett $\rho\sigma$ study of substituent



(**44**)

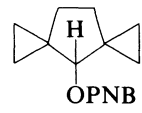


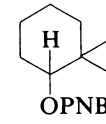


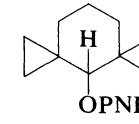
Rel. rates 10^4 10^3 1

effects in the benzene ring gave a good correlation versus σ^+ values with a normal ρ of -3.33 for a secondary cyclopropylmethyl system.

Several secondary dispirocyclopropylcarbinyl systems have been studied by Krapcho and coworkers[128] giving the relative rates in 80% aqueous acetone at 50°C shown. Thus, in both the spiro[2,4] and spiro[2,5] systems the second spiro cyclopropyl group causes an



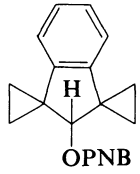




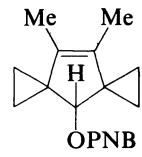
Rel. rates 1 590 0.2 300

additional large increase in rate, although not nearly of the magnitude produced by the first spirocyclopropyl group. Both dispiro systems gave mainly unrearranged dispiranol products.

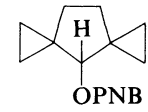
Comparisons of the solvolysis rates in 80% aqueous acetone of the secondary dispiro derivatives **45** and **46** with a suitable model compound **47** revealed only small rate differences despite the possibility of cyclic conjugation involving interaction of a π-system with a biscyclopropylcarbinyl cation[129]. Such an ion might have been anticipated to show unusual stability as a cyclic delocalized six-electron system. The product from the benzo



(45)



(46)

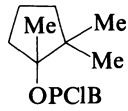


(47)

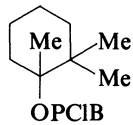
Rel. rates 0.19 15 1.0

system **45** was 90% unrearranged alcohol. The double-bond containing compound **46**, however, gave < 5% unrearranged alcohol.

Studies of spirocyclopropyl stabilization have also been carried out in tertiary spiro[2,4] and spiro[2,5] systems[130-132]. Thus, in 60% aqueous dioxane the following relative rates were observed for some *p*-chlorobenzoate (OPClB) derivatives. No ring-opened products

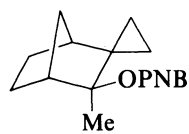


Rel. rates 1 10^4 1

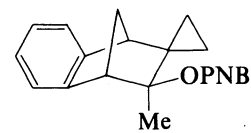


0.1 10^3 0.1

were observed for any of the tertiary spiro systems. The results are of interest in that, although the tertiary spiro systems are about 10^4 more reactive than the secondary spiro systems, the spirocyclopropyl to geminal dimethyl rate ratios are almost as large (10^4) as are those observed for the secondary spiro systems (10^5). A study[132] of 3-spirocyclopropyl substitution has also been done in the tertiary 2-norbornyl and 5,6-benzo-2-norbornyl



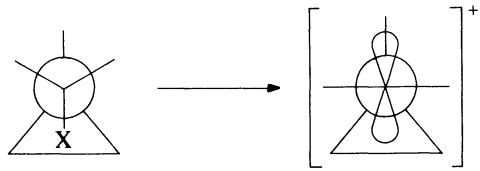
(48)



(49)

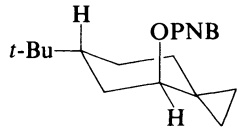
systems **48** and **49**, respectively. In these systems spirocyclopropyl substitution causes rate enhancements of about 10^4.

Of considerable interest have been several investigations directed toward spirocyclopropylcarbinyl systems which are forced into ionizing to a perpendicularly twisted conformation (**50**) rather than to the favored bisected conformation.

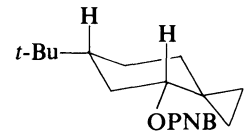


(50)

An early attempt[133, 134] to achieve the perpendicular cyclopropylcarbinyl conformation by means of *t*-butyl-substituted spiro[2,5]octyl derivatives was unsuccessful. Thus, the *cis* isomer (**52**) with the *t*-butyl and leaving groups both equatorial was expected to solvolyze much more slowly than the *trans* isomer (**51**) having an equatorial *t*-butyl group and an axial leaving group. However, the small rate difference of 2:1 revealed that the



(51)

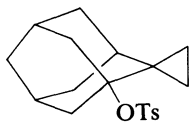


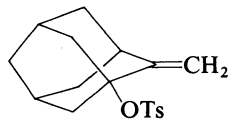
(52)

Rel. rates 2 1

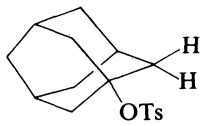
stabilization achieved by bisected cyclopropyl participation with an axial leaving group was large enough to overcome the unfavorable factors of the *cis* isomer having to ionize via a conformation having an axial *t*-butyl group.

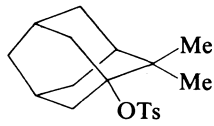
In similar studies by Martin and Ree[135, 137] and Schleyer and Buss[134, 136], which were published simultaneously, the problem of locking the cyclopropylcarbinyl system into the energetically unfavorable perpendicular conformation was solved by use of a spiroadamantyl system. The relative rates shown in Scheme 6 were measured in acetic acid at 45 °C.





Rel. rates 10^{-3} 10^{-6}





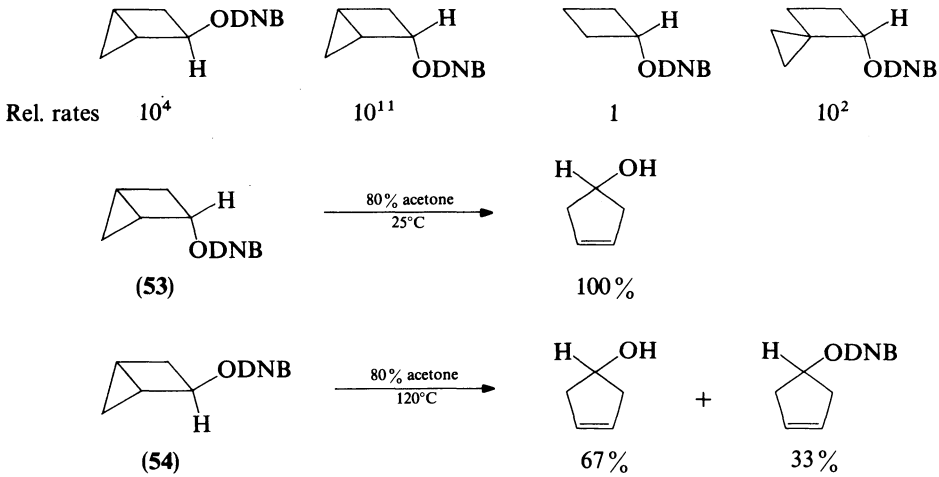
1 2

SCHEME 6. The relative rates of acetolysis of some adamantyl tosylates at 45 °C.

D. 2-Bicyclo[2.1.0] pentyl and Related Systems

An investigation of the hydrolysis rates and products of derivatives of the parent 2-bicyclo[2.1.0]pentyl system was first reported by Wiberg and coworkers in 1968 in a

preliminary communication[138] and later in 1970 in a full paper[139]. The relative rates with some comparisons and products for hydrolysis in 80% aqueous acetone are given in Scheme 7.



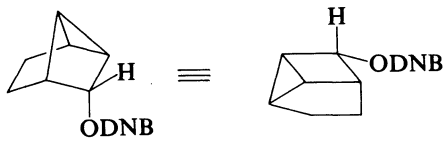
SCHEME 7. The relative rates and products of hydrolysis of the *endo*- and *exo*-2-bicyclo[2.1.0]pentyl 3,5-dinitrobenzoates in 80% aqueous acetone[139]

The high reactivity of the *endo* isomer **53** has been explained as resulting from its being able to undergo concerted disrotatory ring-opening on ionization. The *exo*-isomer (**54**) on

(**53**) (**54**)

the other hand cannot do this and hence shows normal secondary cyclopropylcarbinyl reactivity.

Another system which is not usually considered as a 2-bicyclo[2.1.0]pentyl system but in reality is a 3,5-ethano bridged *endo* derivative is the tricyclo[2.2.1.$0^{3,7}$]hept-2-yl *p*-nitrobenzoate (**55**) shown below[140]. This is related to the *anti*-7-norbornenyl system by

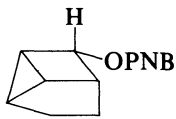


(**55**)

cyclopropylcarbinyl–homoallyl cation rearrangement. The high reactivity of this tricyclic system is thus readily understandable and one can estimate, after correcting for solvent and

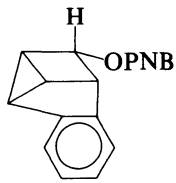
leaving group differences, that it is approximately 1000 times more reactive than the parent *endo*-2-bicyclo[2.1.0]pentyl system **53**. This higher reactivity must be due in part to the presence of the five-ring residue (a factor of 10) and the remainder to effects of additional ring strain and conformational changes.

Although with the tricyclo[2.2.1.0^{3,7}]hept-2-yl system **55** only the *endo* derivative was available, Tufariello and Rowe[141] have prepared both *endo* and *exo* epimers **56** and **57** of the corresponding benzo system. The relative rates given were measured in 80% aqueous acetone at 25 °C.



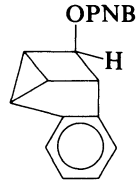
(55)

Rel. rates 1



(56)

10^{-1}



(57)

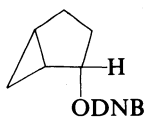
10^{-7}

The slightly lower rate of the *endo*-benzo isomer **56** must be due to an electron-withdrawing inductive effect, and the *endo–exo* rate difference due to the same reasons as for the parent 2-bicyclo[2.1.0]pentyl system[139].

E. 2-Bicyclo[3.1.0]hexyl and Related Systems

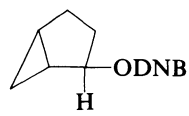
Of all of the parent 2-bicyclo[n.1.0]alkyl systems, the 2-bicyclo[3.1.0]hexyl has been studied with the greatest number of different leaving groups and solvents and in the most laboratories. Thus, the chlorides have been hydrolyzed in 70% aqueous acetone at 25 °C[142], the amines have been deaminated in 70% aqueous acetone at 25 °C[142], the *N*-methyl 4-oxopyridinium iodides have been solvolysed in 80% aqueous ethanol at 86 °C[143, 144], the 3,5-dinitrobenzoates have been hydrolyzed in 80% aqueous acetone at 100 °C[145, 146] and in 60% aqueous acetone at 90 °C[147] and the *p*-toluenesulfonates have been studied in acetic acid at 25 °C[148]. Since the use of 3,5-dinitrobenzoates in 80% aqueous acetone represents standard conditions which are often encountered in studies of cyclopropylcarbinyl systems, only those results obtained under these conditions will be presented here in detail. The results obtained under the other conditions all lead to similar conclusions. A comparison of the products obtained under the various conditions is given in Scheme 8. *Exo* and *endo* leaving groups give essentially the same products.

The relative rates of hydrolysis of the *endo*- and *exo*-2-bicyclo[3.1.0]hexyl 3,5-dinitrobenzoates (**58** and **59**) together with some comparison rate data[122, 149] are given below. The observation that essentially identical rates and products for hydrolysis are



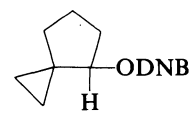
(58)

Rel. rates 1.2

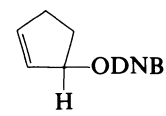


(59)

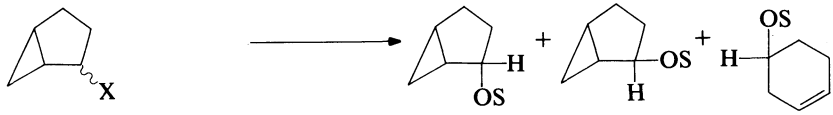
1.0



50



10^3

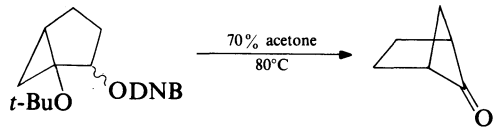


X[Ref]	Conditions		% Yield	
Cl[142]	70% acetone 25 °C	32	55	13
$\overset{+}{N}_2$[142]	70% acetone 25 °C	32	52	16
O-(N-Me$\overset{+}{P}$y)[143, 144]	80% ethanol 86 °C	42	50	8
ODNB[145, 146]	80% acetone 100 °C	36	39	25
ODNB[147]	60% acetone 90 °C	37	48	15
OTs[148]	HOAc, NaOAc 25 °C	17	36	47

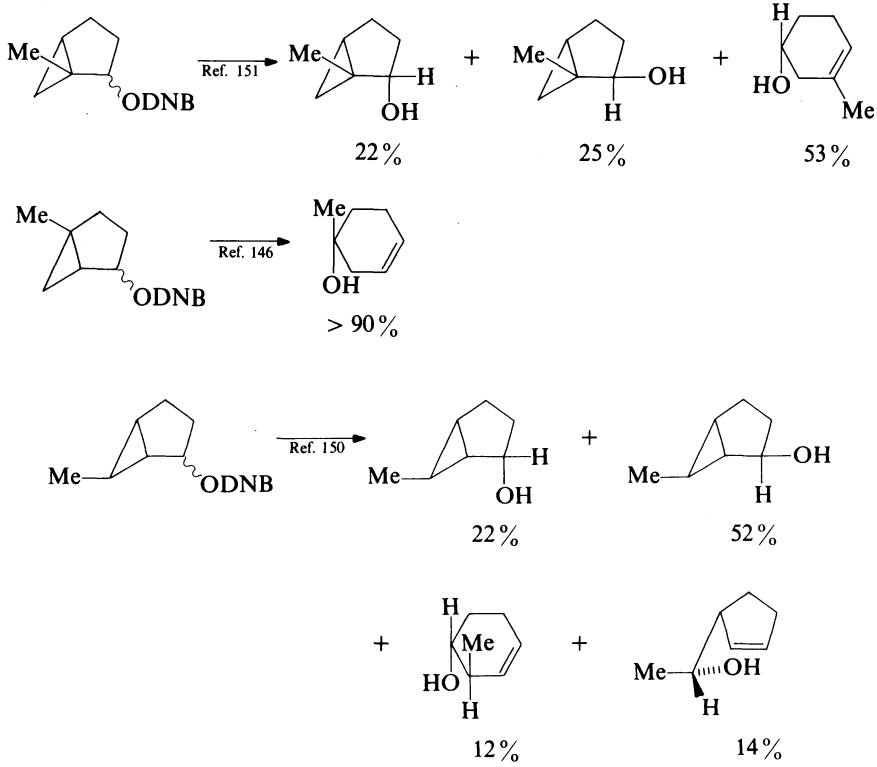
SCHEME 8. A comparison of the products of hydrolysis of different 2-bicyclo[3.1.0]hexyl derivatives under various conditions

obtained from both *exo* and *endo* derivatives indicates that both must be ionizing via bisected cyclopropylcarbinyl-activated complexes to give the same bisected intermediate. This conclusion is supported by the similar behaviors of the *exo*- and *endo*-2-bicyclo[3.1.0]hexyl derivatives with regard to deuterium scrambling via possible cyclopropylcarbinyl–cyclopropylcarbinyl cation rearrangement[146] (none is observed with either epimer), to 5-methyl substituent effects (factors of 18- and 20-fold increase in rate) to *anti*-6-methyl substituent effects[150] (factors of 8.3- and 10-fold increase in rate) and 1-methyl substituent effects[151] (factors of 2.4- and 2.0-fold increase in rate). Some of the products are compared in Scheme 9.

In an investigation stemming from a deamination study in the same system, Kirmse and Alberti[152] examined the solvolyses of the 1-isobutoxy *exo* and *endo*-2-bicyclo[3.1.0]hexyl 3,5-dinitrobenzoates (**60** and **61**) in 70% aqueous acetone. No kinetics were measured, and the only product which could be identified in low yield was bicyclo[2.1.1]hexane-5-one (**62**).



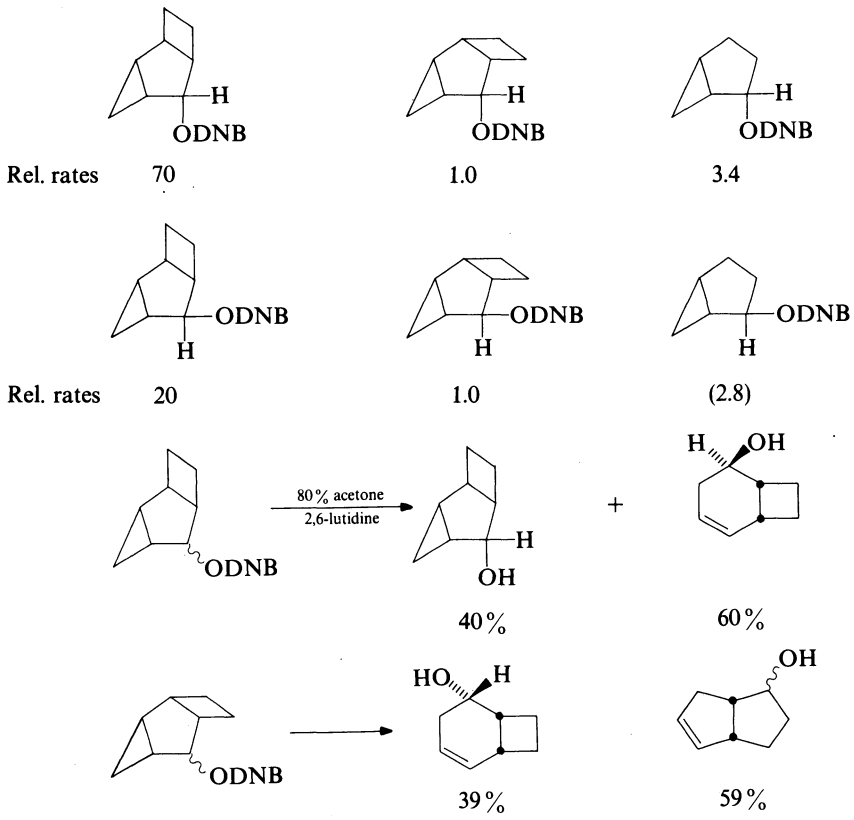
(**60**) and (**61**) (**62**)



SCHEME 9. A comparison of the products of hydrolysis of different methyl-substituted 2-bicyclo[3.1.0]hexyl derivatives in 80% aqueous acetone at 80–100 °C

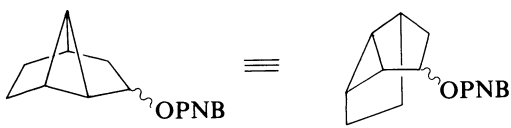
Paquette and coworkers[153, 154] have carried out a solvolytic study of a tricyclic system in which a 3,4-ethano group is attached to the 2-bicyclo[3.1.0]hexyl system. This was done to assess the importance of cyclopropyl versus cyclobutyl neighboring group involvement. Some relative rate data are given in Scheme 10 for 3,5-dinitrobenzoate hydrolyses in 80% aqueous acetone at 115 °C. Product results are also shown. Deuterium labeling revealed the lack of any cyclopropylcarbinyl–cyclopropylcarbinyl cation rearrangements. Also, the results showed that cyclopropyl participation predominates over initial involvement of the cyclobutyl group.

Gassman and coworkers[155] studied several 2-bicyclo[3.1.0]hexyl systems where there was a trimethylene or tetramethylene bridge across the 1,5-carbons. The relative rate and product data given in Scheme 11 for reaction in 70% aqueous acetone reveal that the presence of the bridge affects the *endo* and *exo* isomers similarly. The change in products on going from the trimethylene to the tetramethylene bridge must be related to steric differences and to having a bridgehead double bond in a [4.3.1] system versus a [3.3.1] system.



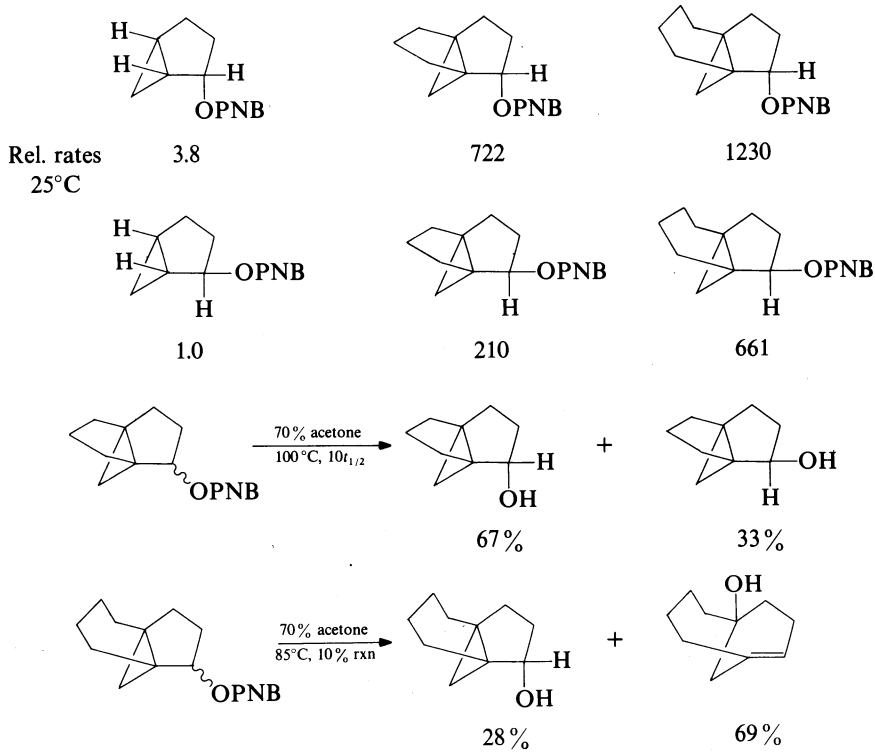
SCHEME 10. The relative rates and products of hydrolyses of some isomeric 3,4-ethano bridged 2-bicyclo[3.1.0]hexyl *p*-nitrobenzoates in 80% aqueous acetone[153, 154]

Several tricyclic systems which are not usually treated as 2-bicyclo[3.1.0]hexyl derivatives, but which should be included in this section are as follows. The solvolyses of the *exo* and *endo* tricyclo[3.3.0.$0^{2,8}$]oct-3-yl *p*-nitrobenzoates (**63** and **64**) were examined by Johnson and coworkers[156a] in 70% aqueous acetone at 100°C. The relative rates and products of reaction are given in Scheme 12. It is seen that with the exception of higher *endo*-product selectivity, the behavior of this system is similar to that for the parent system.



(**63**) and (**64**)

The unexpected *endo* selectivity has been explained by Bach and coworkers[156b] as evidence for a nonplanar carbonium ion.

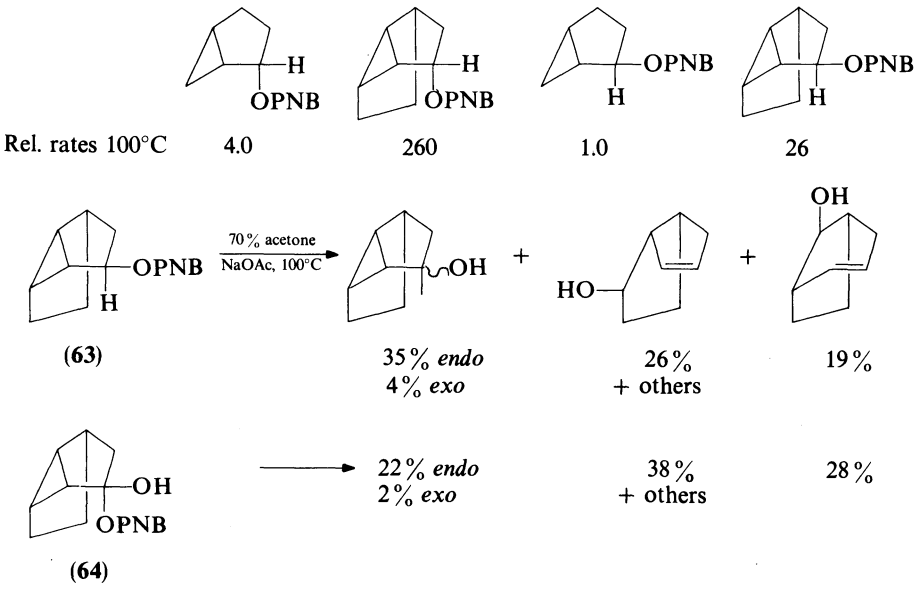


SCHEME 11. The relative rates and products of hydrolysis of some 1,5-bridged 2-bicyclo[3.1.0]hexyl *p*-nitrobenzoates in 70% aqueous acetone[155]

Another place in which a 2-bicyclo[3.1.0]hexyl moiety is incorporated within a tricyclic system is with the tricyclo[3.2.0.0^{2,7}]hept-3-yl derivatives **65** and **66** studied by

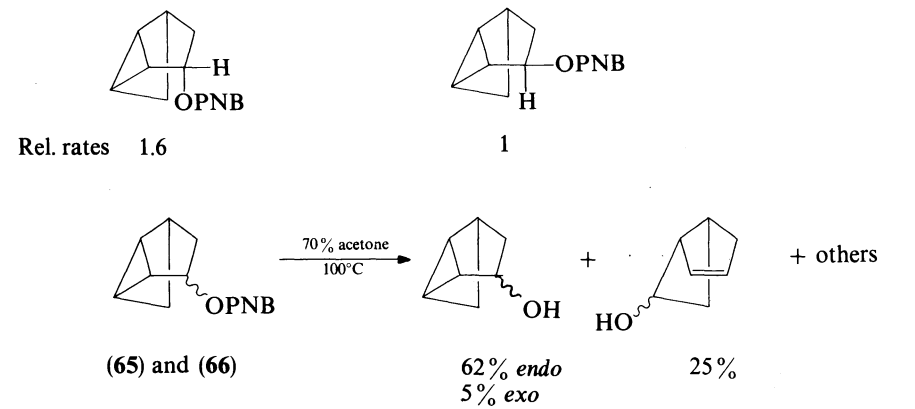
(**65**) and (**66**)

Lustgarten[157]. The relative rates and products of hydrolysis in 80% aqueous acetone at 100°C are given as follows. Again high *endo*-product selectivity is evidenced. It should be noted that the rates of reaction for **65** and **66** are similar ($k_{exo} = 2.94 \times 10^{-5}$ s^{-1}; $k_{endo} = 4.59 \times 10^{-5}$ s^{-1} at 99.6°C) to those for the homologous 4,6-ethano bridged systems **63** and **64** studied by Johnson and coworkers[156a] ($k_{exo} = 1.63 \times 10^{-5}$ s^{-1}; $k_{endo} = 16.5 \times 10^{-5}$ s^{-1} at 101.0°C) in the same solvent. It is interesting however, that whereas Johnson and coworders[156a] reported cyclopropylcarbinyl–allylcarbinyl ring-opening to both

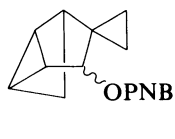


SCHEME 12. The relative rates and products of hydrolysis of the *endo*- and *exo*-tricyclo[3.3.0.0^{2,8}]oct-3-yl *p*-nitrobenzoates in 70% aqueous acetone[156a]

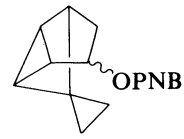
[3.3.0] and [3.2.1]octyl systems, in Lustgarten's work only [3.2.0]heptyl and no [2.1.1]heptyl products were obtained. This must be a ring size effect.



A study closely related to the previous except that the 2-bicyclo[3.1.0]hexyl system also contained a 3-spirocyclopropane as in **67** or a spirocyclopropane on the bridging methylene as in **68** was carried out by Ipaktschi and coworkers[158]. The rates and products

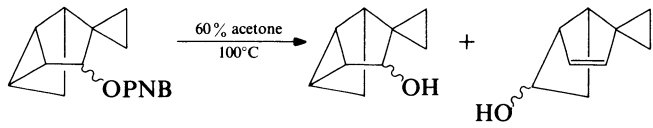


(67)

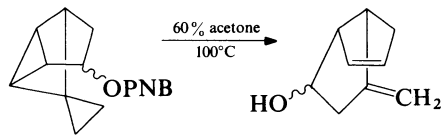


(68)

of hydrolysis of both *exo* and *endo* leaving groups were studied for each system in 60% aqueous acetone. In both systems the *exo* and *endo* isomers exhibited similar reactivities and products. Compared to the parent compounds **65** and **66** studied by Lustgarten[157],



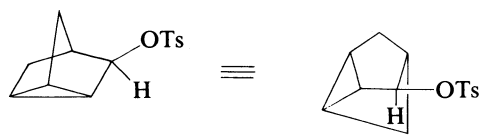
(67) 40% 60%



(68) 80%

the spirocyclopropane on the bridging methylene in **68** had a negligible influence on the rate. However, the 3-spirocyclopropane in **67** caused approximately a 100-fold rate acceleration.

The nortricyclyl system **69** has been of interest for many years[159a] because even though it is formally a 2-bicyclo[3.1.0]hexyl derivative, it has a surprisingly low reactivity. This



(69)

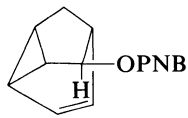
may be explained, however, as being related to the difficulty for the carbinyl carbon in the strained system to achieve trigonal geometry. That the cyclopropyl ring in the nortricyclyl

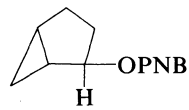
(69)

Rel. rates HOAc	1.0	10^5

system is still, however, exerting a strong electron-releasing resonance effect to the cationic center was shown in a $\rho\sigma$ study of 3-aryl-3-nortricyclyl *p*-nitrobenzoates by Brown and Peters[159] where a ρ^+ value of -3.27 was found for hydrolysis in 80% acetone. The corresponding ρ^+ for 7-aryl-7-norbornyl derivatives was -5.27.

Diaz and coworkers[160] have investigated the solvolysis of a related system **70** in which, however, the 3,6-methano bridge of the nortricyclyl system is replaced by a 3,6-etheno bridge. Relative rates are given for hydrolysis in 80% aqueous acetone at 100 °C. Products



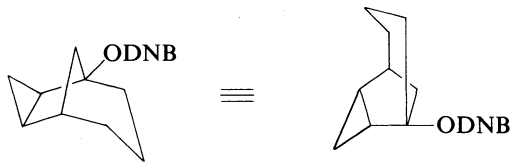


(70)

Rel. rates	1.0	24

were determined in 60% aqueous acetone at 100 °C and found to be almost exclusively the alcohol of retained structure. It is observed that here, where the ring strain in the system is reduced, the rate of hydrolysis is not greatly different from that for the parent [3.1.0] system.

As part of their key study of the reactivities of geometrically constrained cyclopropylcarbinyl systems, Rhodes and DiFate[161] examined the solvolysis of the 2,4-trimethylene bridged 2-bicyclo[3.1.0]hexyl 3,5-dinitrobenzoate (**71**) in 50% ethanol. There is no other

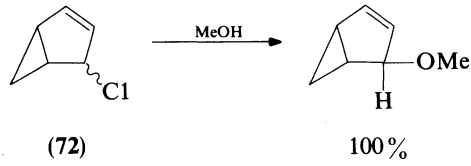


(71)

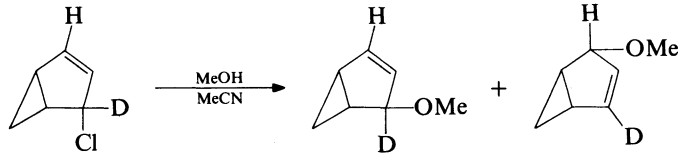
2-bicyclo[3.1.0]hexyl system which can be used for ready rate comparisons. In Rhodes and DiFate's paper[161] they estimated that the cyclopropane caused a rate enhancement of 4×10^5 at 25 °C over the rate for the corresponding non-cyclopropanated 1-bicyclo[3.2.1]octyl system.

It is finally of interest to consider the solvolytic chemistry of 3,4-unsaturated and 3,4-benzo 2-bicyclo[3.1.0]hexyl systems. These are of special interest because they are sources of homologs of the antiaromatic cyclopentadienyl and inden-1-yl cations and as such should be destabilized antihomoaromatic systems.

The bicyclo[3.1.0]hex-3-en-2-yl chloride system **72** has been studied by Berson and Hasty[162]. Although solvolytic kinetics were not run, products and deuterium scrambling were examined. The predominance of the *exo*- solvolysis product may be due to an antihomoaromatic effect in which only the *endo* side of the p orbital at C(2) interacts with the cyclopropane ring. Solvolytic chemistry in the bicyclo[3.1.0]hex-3-en-2-yl system has also been discussed by Cueille and Jullien[163].



(72) 100%

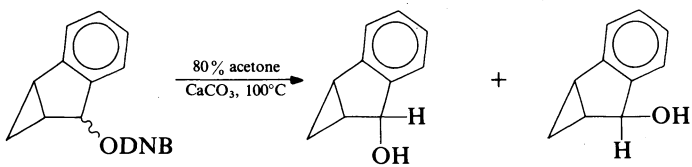


50% 50%

Solvolytic studies in the 3,4-benzo -2-bicyclo[3.1.0]hexyl system have been quite extensive[151, 164–166]. The *endo*- and *exo*-3,5-dinitrobenzoates **73** and **74** have been found to react at essentially identical rates in 80% aqueous acetone. Also, both have been found

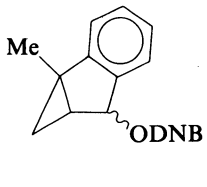
(73) (74)

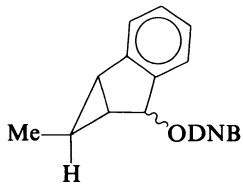
to give essentially identical product mixtures. Kinetic comparisons with model systems reveal that the benzo systems are about 1000 times less reactive due to antihomoaromatic interactions. The predominance of *exo*-solvolysis product is similar to that observed in the



(73) or (74) 20% 80%

bicyclo[3.1.0]hex-3-en-2-yl system[162]. Substitution of methyl groups at C(5) and C(6) in the 3,4-benzobicyclo[3.1.0]hexyl system gave the methyl substituent effects shown[165] for solvolysis in 80% aqueous acetone. These results support an electronic argument for the *exo*-product preference in solvolysis. The larger 6-methyl substituent effect is in accord with the *endo* side of the p orbital at carbon-2 in the activated complex being more involved in bonding with the cyclopropane ring and consequently being less available for solvent attack.

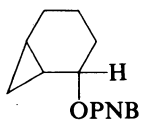


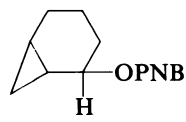


	exo or *endo*	*exo* or *endo*
k Me/H 100°C	1.1	17

F. 2-Bicyclo[4.1.0]heptyl and Related Systems

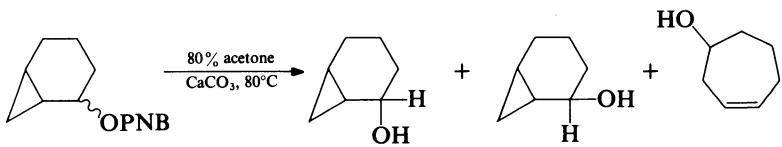
Studies of the rates and products of hydrolysis of *endo*-and *exo*-2-bicyclo[4.1.0]heptyl derivatives **75** and **76** were first reported in preliminary form by Goering and Rubenstein[167] and later in more detail by others[168–170]. The relative rates below for reactions in 80% aqueous acetone at 80°C[169] reveal that as with the 2-bicyclo[3.1.0]hexyl system (k[4.1.0] = ca.150k[3.1.0]) reaction rates are essentially independent of leaving group geometry. This indicates that both *exo* and *endo* isomers can ionize through bisected





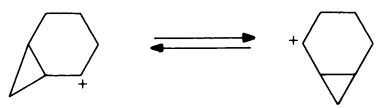
	(75)	(76)
Rel. rates	1.0	1.3

activated complexes. Identical product distributions are also found from the *exo* and *endo* isomers[167].



(75) or (76)	67%	23%	10%

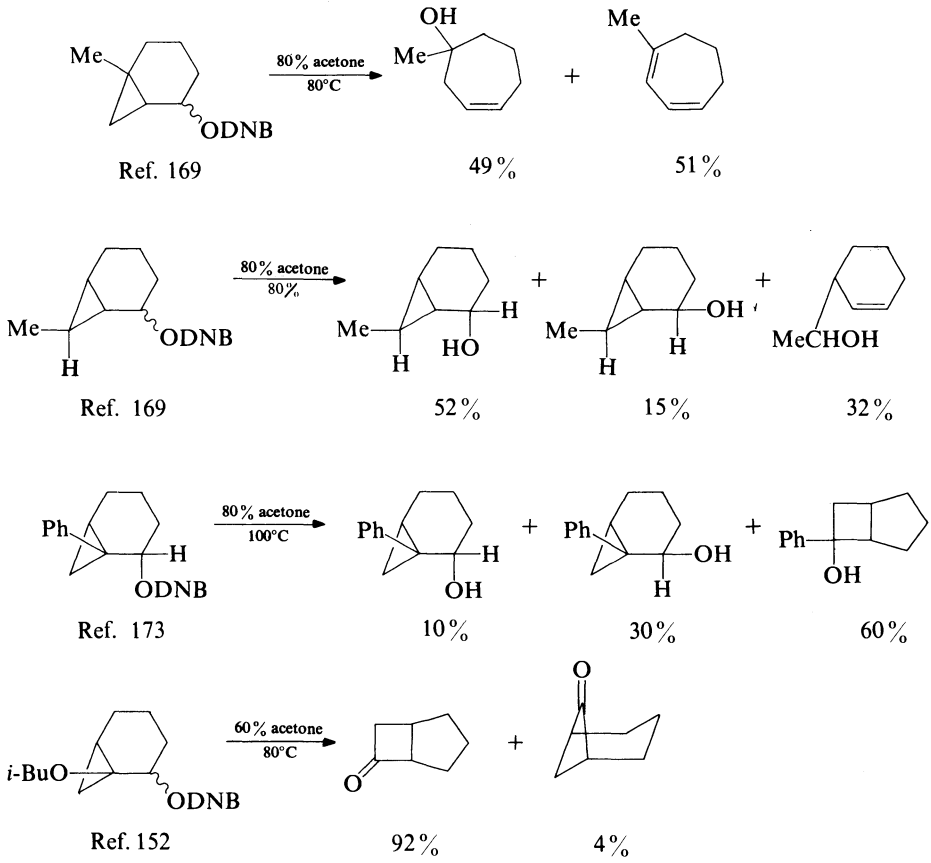
Deuterium-labelling studies[168] revealed that no more than a few percent cyclopropylcarbinyl–cyclopropylcarbinyl cation rearrangement[172] takes place in the parent 2-bicyclo[4.1.0]heptyl system. However, acid-catalyzed alcohol rearrangement and



3,5-dinitrobenzoate solvolysis studies[169,171,173] revealed that 1-methyl substitution increased the amount of the rearrangement while 2,6 or *anti*-7-methyl substitution caused it to decrease.

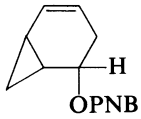
For the various methyl-substituted 2-bicyclo[4.1.0]heptyl 3,5-dinitrobenzoates[169,173], in all cases the *exo* isomers were slightly more reactive than the *endo*. The k_{Me}/k_H values for the various methyl substituents, which were as expected based on studies involving open-chain cyclopropylcarbinyl systems[99], were: 1-methyl = 2; 2-methyl = 10^5; 6-methyl = 10; *anti*-7-methyl = 6. In a study using a 1-phenyl substituent[173], a rate decrease by a factor of about 10 was observed. This may be due in part to electron-withdrawing inductive effects of the phenyl group and in part to steric hindrance to solvation for the cyclopropylcarbinyl system.

The hydrolysis products in 80% acetone for the 1-methyl-substituted 2-bicyclo[4.1.0]heptyl 3,5-dinitrobenzoates were not markedly different from those of the parent system. However, substitution of 6- and 7-methyl groups[169], as well as a 1-phenyl group[173] or a 1-isobutoxy group[152] produced major changes in product distributions as shown in Scheme 13.

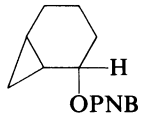


SCHEME 13. Effects of substituents on product distributions from hydrolysis of 2-bicyclo[4.1.0]heptyl 3,5-dinitrobenzoates

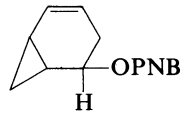
Gassman and Creary[170] besides studying the parent 2-bicyclo[4.1.0]heptyl derivatives **75** and **76**, also examined the effects of introducing a 4,5-double bond as in **77** and **78**. The relative rates given below were for *p*-nitrobenzoate hydrolysis in 70% acetone at 100°C, and



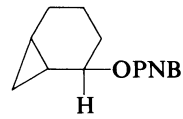
(**77**)



(**75**)



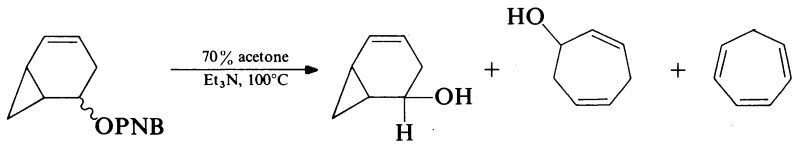
(**78**)



(**76**)

Rel. rates	1.1	15	1.0	17

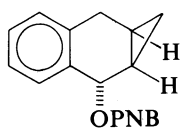
reveal the operation of an electron-withdrawing inductive effect by the double bond. The products for the *exo*- and *endo*-unsaturated systems were both as follows.

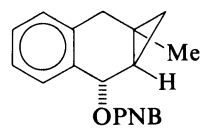


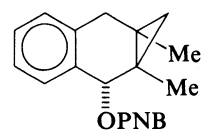
(**77**) or (**78**)	7%	30%	63%

Yano and coworkers[174–176] have studied the solvolyses of the 2-bicyclo[4.1.0]heptyl systems **79** and **80** in which the cyclopropane is incorporated as part of a bicyclobutane moiety. Some relative rate and product data are given in Scheme 14 together with a possible mechanistic rationalization for the products formed using non-delocalized intermediates for simplicity.

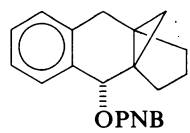
Several studies of benzobicyclo[4.1.0]heptyl systems have appeared[165,177–180]. Some relative rates for *p*-nitrobenzoate hydrolysis in 80% aqueous acetone are given below. The





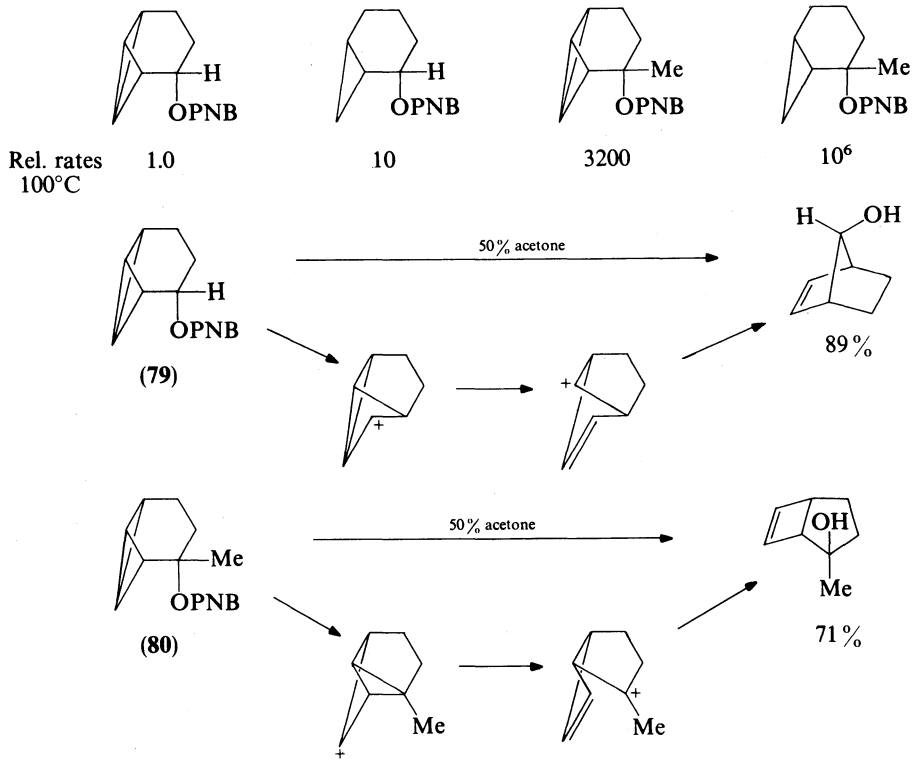


Rel. rates 25°C	1.0	3.2	10



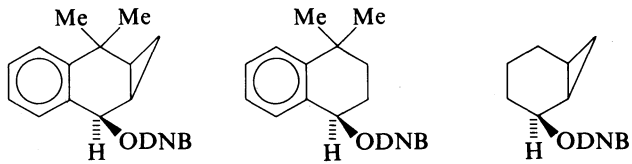
13

products ranged from 100% benzobicyclo[4.1.0]hepten-2-ol for the non-methyl-substituted compound to 100% benzocycloheptadienol product for the dimethyl-substituted compound[180]. Some additional important relative rates for the



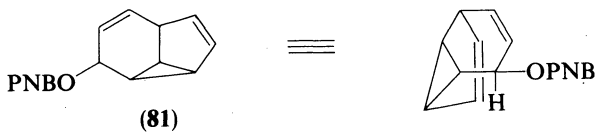
SCHEME 14. The relative rates and products of hydrolysis of some bicyclobutylcarbinyl *p*-nitrobenzoates in 50% aqueous acetone[174–176]

benzobicyclo[4.1.0]heptenyl system were reported by Friedrich and coworkers[165] for 3,5-dinitrobenzoate hydrolysis in 80% aqueous acetone.



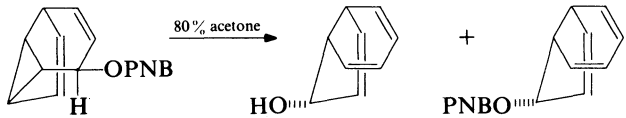
Rel. rates 80°C 2400 1.0 18

The homosemibullvalenyl system(**81**) is in reality a 5,7-etheno bridged bicyclo[4.1.0]hept-3-en-2-yl derivative[181]. Its rate of hydrolysis has been measured in 80%



(**81**)

aqueous acetone at 75°C and appears to be normal for an allylic 2-bicyclo[4.1.0]heptyl system. The products are as follows, with the rearranged *p*-nitrobenzoate arising through ion pair return.



(**81**) 67% 33%

As part of their study of geometrically constrained cyclopropylcarbinyl systems, Rhodes and DiFate[161] studied a tertiary 2,5-ethano bridged 2-bicyclo[4.1.0]heptyl tosylate (**82**).

(**82**)

An interesting rate comparison is with the corresponding trimethylene bridged [4.1.0] system (**83**)[180].

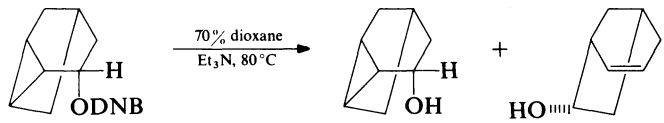
(**82**) (**83**)

Rel. rates 1.0 4.3

A 4,7-methylene bridged 2-bicyclo[4.1.0]hexyl 2,4-dinitrobenzoate (**84**) has been investigated by Grob and coworkers[182,183]. The rates and products of reaction of **84** were

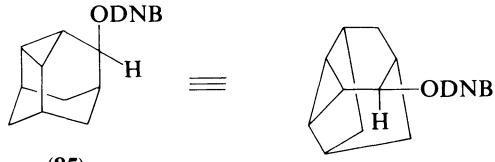
(**84**)

determined in 70% dioxane. One can estimate[170] its rate of hydrolysis as being approximately 100 times faster than that of the parent 2-bicyclo[4.1.0]heptyl system(**75**).



(**84**) 77% 23%

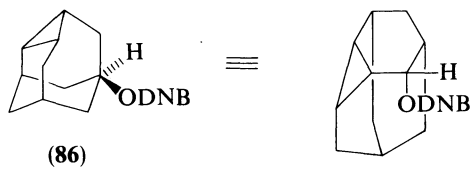
Finally, several systems which are more commonly thought of as dehydroadamantyl or dehydrohomoadamantyl systems may also be considered as 2-bicyclo[4.1.0]heptyl derivatives. For the case of the 8,9-dehydro-2-adamantyl 3,5-dinitrobenzoate (**85**),



(**85**)

solvolysis in 60% aqueous acetone gave only the 8,9-dehydro-2-adamantol as the product[184]. A similar product run in which the starting material was 2-deuterated or 2-tritiated gave product in which the label was completely scrambled over the 2, 8 and 9 carbons by cyclopropylcarbinyl–cyclopropylcarbinyl cation rearrangement. The rates of solvolysis for the 8,9-dehydro-2-adamantyl 3,5-dinitrobenzoate were measured in 60% aqueous acetone. Rate comparisons in the paper were made to the 1-methylcyclopropylcarbinyl system which is approximately 1000 times less reactive. However, a better comparison may be with Grob's[182,183] 4,7-methylene bridged 2-bicyclo[4.1.0]hexyl 3,5-dinitrobenzoate (**84**) mentioned earlier which under similar conditions can be estimated to react at a rate which is comparable with that of the 8,9-dehydro-2-adamantyl system (**85**).

Another adamantyl system which has recently been studied by Harris and coworkers[185] is the *endo*-2,4-dehydro-5-homoadamantyl 3,5-dinitrobenzoate (**86**). The product from

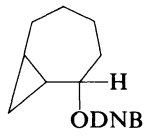


(**86**)

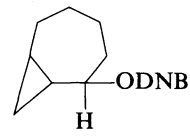
hydrolysis of **86** in 70% aqueous acetone was 87% alcohol of retained structure and stereochemistry. The reaction rate was also measured in 70% aqueous acetone and compared with various non-cyclopropyl-containing systems. Its rate ($k_1 = 3.35 \times 10^{-4}$ s^{-1} in 70% acetone at 100°C) can be estimated to be almost identical to that of the corresponding 8,9-dehydro-2-adamantyl 3,5-dinitrobenzoate (**85**) ($k_1 = 3.03 \times 10^{-3}$ s^{-1} in 60% aqueous acetone at 100°C) mentioned earlier[184].

G. 2-Bicyclo[5.1.0]octyl and Related Systems

The first studies in the 2-bicyclo[5.1.0]octyl system were reported by Cope and coworkers[186]. However, they did not measure any reaction kinetics, and product studies were done under conditions where the initial products were not stable. Later in 1969, Friedrich and Wight[187] studied the rates and products of hydrolyses of the *endo*- and *exo*-2-bicyclo[5.1.0]octyl 3,5-dinitrobenzoates **87** and **88** in 80% acetone. In contrast to the behavior seen with the [3.1.0]hexyl and [4.1.0]heptyl systems where rates and products are essentially independent of leaving group stereochemistry, the *endo*-2-bicyclo[5.1.0]octyl 3,5-dinitrobenzoate (**87**) reacts 24 times faster than does the *exo* isomer (**88**). Both are,



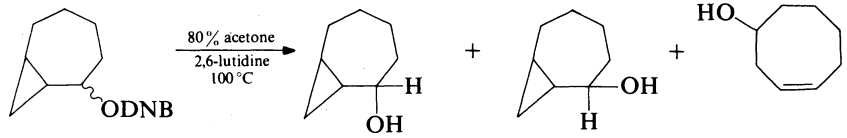
(87)



(88)

Rel. rates	24	1.0

however, less reactive than the corresponding [4.1.0]heptyl derivatives **75** and **76** (*endo*- is 2.8 times slower, *exo*- is 74 times slower). Also, the *exo*- and *endo*-[5.1.0]octyl 3,5-dinitrobenzoates give different hydrolysis product mixtures. Polarometric and deuterium



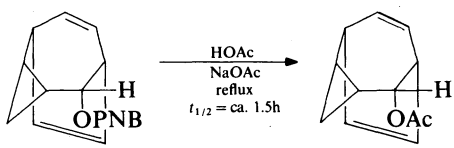
(87) or (88)

endo-	56%	19%	25%
exo-	52%	35%	13%

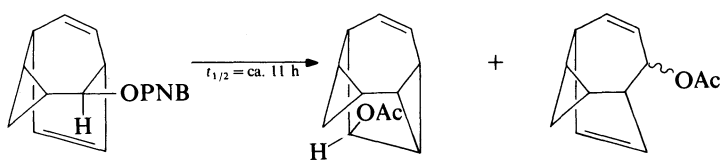
scrambling studies on these systems showed that the cationic intermediate from the *endo* system does not scramble or racemize by cyclopropylcarbinyl–cyclopropylcarbinyl cation rearrangement. However, that from the *exo* system does. Friedrich and Wight[187] suggested that these results point to two, probably conformationally different, bisected cyclopropylcarbinyl cation intermediates being involved at least in part in the reactions in this system. However, possible structures for these were not provided.

The only other [5.1.0] derivatives which appear to have been studied are the tricyclic compounds **89** and **90** shown below[188]. Reaction half-lives and products for **89** and **90** are

(89) and (90)



(89) >95%



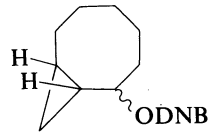
(90) 22% 74%

also shown. It appears that in the *endo* system (**89**) cyclopropyl participation predominates over double-bond participation. However, in the *exo* system (**90**) double-bond participation controls the products.

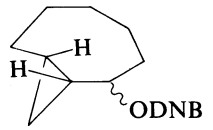
H. 2-Bicyclo[6.1.0]nonyl Systems

Both the *cis* and *trans* ring-fused 2-bicyclo[6.1.0]nonyl systems have received the simultaneous attention of several different research groups[189–191]. Although different leaving groups and reaction solvents were used in the different studies, the conclusions reached were basically the same. Therefore, since the 3,5-dinitrobenzoate leaving group and 80% acetone solvent used by Wiberg and Nakahira[190] are those most often encountered in 2-bicyclo[n.1.0]alkyl system studies, the data quoted in this review will be mostly theirs.

The relative rates of solvolyses of the four isomeric 2-bicyclo[6.1.0]nonyl 3,5-dinitrobenzoates in 80% aqueous acetone are indicated below[190]. For the *cis* ring-fused [6.1.0] derivatives **91** and **92**, the rates of solvolysis are approximately half as fast as those of the corresponding [5.1.0] derivatives **87** and **88**. As observed in the [5.1.0]system, *endo*



(**91**) and (**92**)



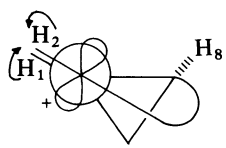
(**93**) and (**94**)

Rel. rates 100°C	*endo* 1.4×10^3	*endo* 1.0
	exo 65	*exo* 1.8×10^4

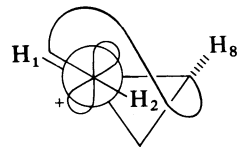
and *exo* isomers in the [6.1.0] system exhibit different rate behaviors. Also, as seen in Scheme 15, they give completely different products with no crossover between systems. Retention of structure is dominant in product formation for all of the isomeric [6.1.0]nonyl systems except with the *trans* ring-fused *endo* compound **93**. In the case of the *trans* ring-fused *endo* system, tosylate results are given because the products were not stable under conditions necessary for the slow 3,5-dinitrobenzoate reaction. The cyclononenol product is formed only from the *endo*-derivatives **91** and **93** because in a cyclononenol from the *exo*-derivatives **92** and **94** the double bond would have to be *trans*.

Wiberg and Nakahira[190] also looked for evidence of cyclopropylcarbinyl–cyclopropylcarbinyl cation rearrangements in all of the systems by deuterium scrambling at the 2-position but found none except with the *trans* ring-fused *exo* system (**94**).

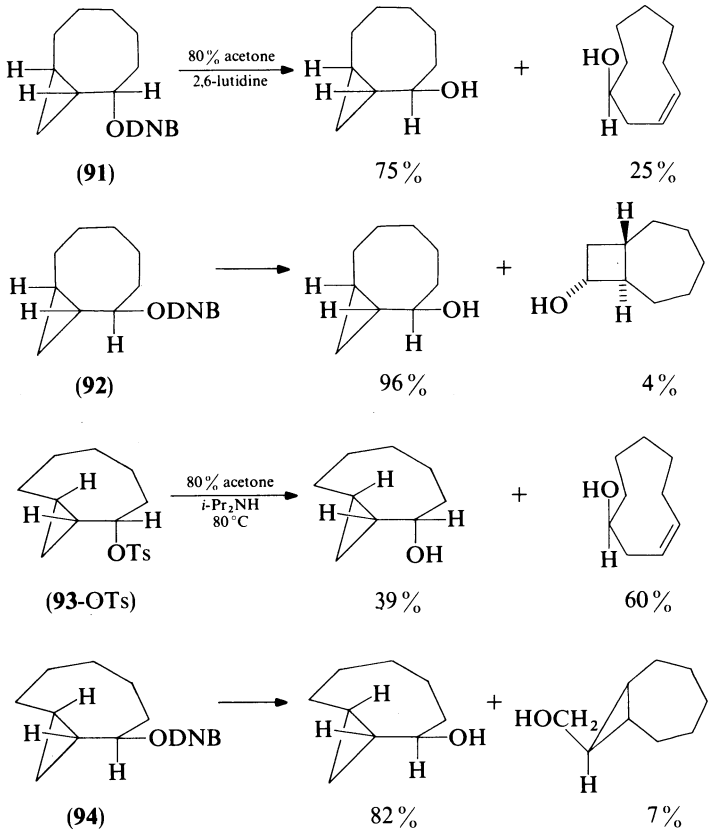
Very recently, Friedrich and coworkers[192] examined *anti*-9-methyl substituent effects and found k_{Me}/k_H rate acceleration in 80% aqueous acetone for *cis* ring-fused 3,5-dinitrobenzoates of 4.7 for the *endo* system **91** and 1.8 for the *exo* system **92**. Thus, with the *cis* ring-fused systems it is suggested that for both *endo* and *exo* leaving groups the



from *endo*-(**91**)



from *exo*-(**92**)



SCHEME 15. Products from hydrolysis of *cis* and *trans* ring-fused *endo*- and *exo*-2-bicyclo[6.1.0]nonyl 3,5-dinitrobenzoates LH, *p*-nitrobenzoates[189, 190] or tosylates[190]

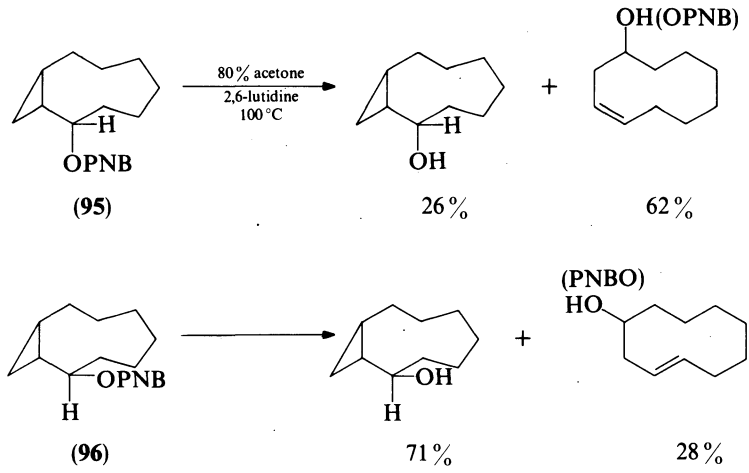
activated complexes and intermediates involved in the reactions are of the bisected type, but that steric effects control reaction stereoselectivity[192].

In the *trans* ring-fused system, on the other hand, the very large reactivity difference suggests that the *exo* isomer **94** can react via a bisected conformation, but the *endo* isomer **93** may be forced into the less-favorable, close-to-perpendicular geometry.

from *endo*-(**93**) from *exo*-(**94**)

I. 2-Bicyclo[7.1.0]decyl and Higher Systems

The parent *cis* ring-fused *endo*- and *exo*-2-bicyclo[7.1.0]decyl *p*-nitrobenzoates **95** and **96** were studied in 80% acetone by Poulter and Winstein[193] and gave kinetic results which paralleled those seen in the *cis* ring-fused [6.1.0] system. The *endo*-[7.1.0] isomer **95** is approximately 17 times more reactive than the *exo*-[7.1.0] isomer **96**, although both [7.1.0] systems are about 50 times more reactive than the corresponding [6.1.0] systems **91**



and **92**. A comparison of the reactivities of all of the 2-bicyclo[2.1.0]pentyl to [7.1.0]nonyl nitrobenzoates is given in Table 1. The product results for the [7.1.0] system also parallel those for the [6.1.0] system in that no crossover between *endo* and *exo* products is seen. However, with the [7.1.0] system a *trans*-cyclodecenol product becomes possible. Both *cis*- and *trans*-cyclodecenols were accompanied by corresponding cyclodecenyl *p*-nitrobenzoates resulting from ion-pair return. Such ion-pair return in a solvolysis is

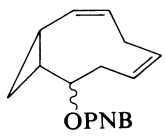
TABLE 1. Rates of solvolysis of some 2-bicyclo[n.l.O]alkyl 3,5-dinitrobenzoate esters in 80% aqueous acetone at 100 °C

Compound	$10^5 k_1$ (s^{-1})	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (eu)	k_{endo}/k_{exo}	k_{rel}	Ref.
endo[2.1.0]	5.80×10^5[a]	16.9	−10	3×10^5	5.04×10^5	139
exo[2.1.0]	1.95[a]	28.4	−4		1.7	139
endo[3.1.0]	1.24	24.2	−16	1.08	1.08	146
exo[3.1.0]	1.15	26.1	−12		1.00	146
endo[4.1.0]	149[a]	26.4	−2	0.80	130	169
exo[4.1.0]	186[a]	24.5	−6		162	169
endo[5.1.0]	50.7[a]	28.9	+2.9	24	44.0	187
exo[5.1.0]	2.10[a]	24.1	−15.8		1.83	187
endo[6.1.0]	22.3	26.5	−5	22.3	19.4	190
exo[6.1.0]	0.999[a]	26.4	−11		0.87	190
endo[7.1.0]	894[b]	21.6	−15.5	17.0	775	193
exo[7.1.0]	52.6[b]	24.9	−12.3		45.7	193

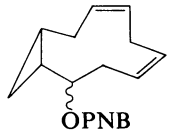
[a] Calculated from data at different temperatures using the experimental thermodynamic parameters provided.
[b] A rate factor of 12 was used to convert *p*-nitrobenzoate to 3,5-dinitrobenzoate data.

usually considered to be indicative of an especially stable delocalized carbocation intermediate.

In the course of their studies of homoallylic ring expansions, Winstein and coworkers[194,195] also examined the hydrolyses of a number of other 2-bicyclo[7.1.0]decyl and 2-bicyclo[8.1.0]undecyl systems. Several of these systems are summarized below and their rates compared with the parent [7.1.0] system.

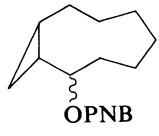


endo	*exo*
0.43	0.089



endo	*exo*
2.2	0.27

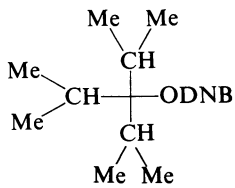
Rel. rates 75°C in 80% acetone

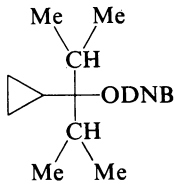


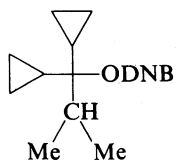
endo	*exo*
23	1.0

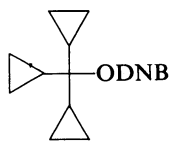
J. Bis- and Triscyclopropylcarbinyl Systems (Non-spiro)

A number of studies have been carried out on systems in which more than one cyclopropane ring is attached to a potential carbocation center. One of the first of these was by Hart and coworkers[196–198] with simple open-chain cyclopropylcarbinyl derivatives. Some of their relative rate data for hydrolysis in 80% aqueous dioxane are as follows.





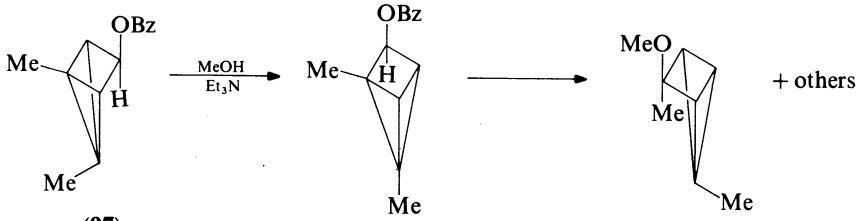




Rel. rates 60°C	1	2.4×10^2	2.4×10^4	2.4×10^7

Thus, it is seen that additional cyclopropyl groups are effective at further stabilizing an adjacent carbocation center.

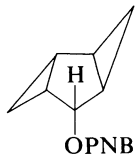
An interesting example of a biscyclopropylcarbinyl system where the leaving group is on a four-membered ring is provided in the work of Masamune and coworkers[199]. The first step in the solvolysis of the 1,5-dimethyltricyclo[2.1.0.$0^{2,5}$]pent-3-yl benzoate (**97**) is very rapid even at $-10°C$ ($k_1 = 4.3 \times 10^{-4}\,s^{-1}$). The authors state that the retained ring skeleton in the product shows that the reaction is very rapid not because of relief of strain



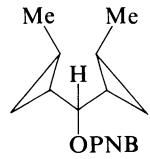
(97)

but because of the unique type of biscyclopropylcarbinyl cation stabilization which can take place.

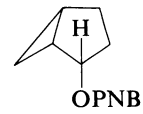
Gajewski and Shih[200] have studied a biscyclopropylcarbinyl system **98** arrayed around a five-membered ring. The rate of hydrolysis of **98** in 90% aqueous acetone was reported to



(98)



(99)

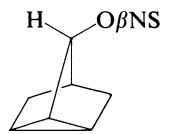


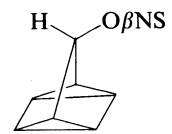
(58)

Rel. rates 25°C	10^4	10^6	1

be unexpectedly slow by comparison with that of the open-chain system **99**. However, comparison with the 2-bicyclo[3.1.0]hexyl system **58** reveals a large rate acceleration produced by the second cyclopropyl group.

In a different biscyclopropylcarbinyl system encompassing a five-membered ring, the quadricyclyl system (**100**), the effect of the second cyclopropane ring is not so pronounced[201, 202]. The relative rates given are for β-naphthalenesulfonate (OβNS) acetolysis at 25°C. Richey and Buckley[201] have suggested as an explanation that the



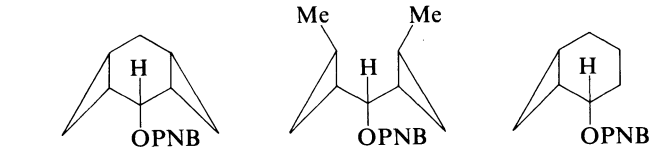


(100)

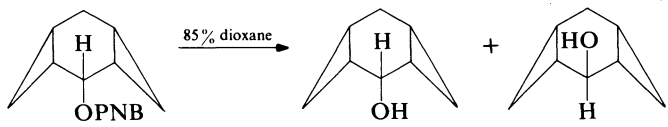
Rel. rates	1	16

attachment of the two cyclopropane rings together or face to face may reduce their ability to delocalize positive charge.

A number of different biscyclopropylcarbinyl systems around a six-membered ring have been studied. Lambert and coworkers[203] have investigated the solvolysis of the cis–cis-tricyclo[5.1.0.$0^{3,5}$]octan-2-yl *p*-nitrobenzoate (**101**) in 85% dioxane.

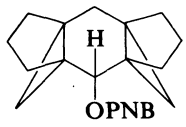


Rel. rates 3×10^4 3×10^4 1

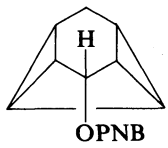


(101) 79% 20%

A similar system (**102**), studied much earlier by Winstein and coworkers[204], which was found to be about 30 times more reactive than **101** and also to give unrearranged product, is shown below. On the other hand, an additional related system **103** also studied earlier by Winstein and coworkers[205] reacted 104 times slower than **101**, Lambert's system[203]. This

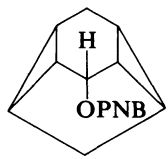


(102)



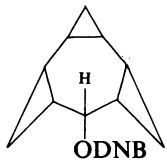
(103)

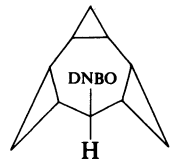
may be due to the same problem which makes the quadricyclyl system **100** so unreactive[201]. In accord with the explanation is the report[206] that the homologous tetracyclo[3.3.1.$0^{2,8}$.$0^{4,6}$]nonan-3-yl (triasteryl) system **104** is highly reactive.

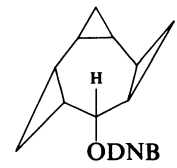


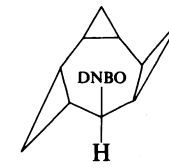
(104)

In the course of an unsuccessful search for the *tris*-σ-homotropylium cation, Ohkata and Paquette[207] studied several biscyclopropylcarbinyl systems around a seven-membered ring. Some of their relative rate data for 3,5-dinitrobenzoate solvolyses in 80% aqueous acetone at 25°C are given below.

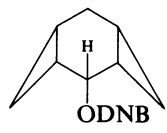


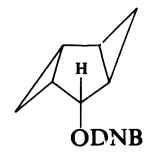






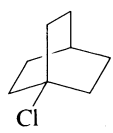
Rel. rates 860 1.0 4 3

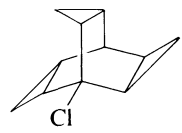


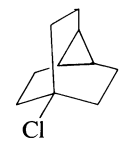


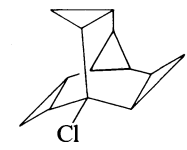
10^5 10^3

Finally, de Meijere and coworkers[208–211] have studied the reactivities of some bridgehead substituted trishomobarrelene and trishomobullvalene derivatives. These are triscyclopropylcarbinyl systems. The relative rates of solvolysis below are for reactions in 80% aqueous dioxane at 25°C[210]. In both systems the cyclopropyl substitution results in





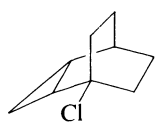


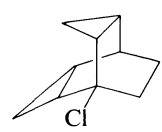


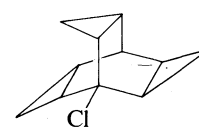
Rel. Rates 1.0 2.7×10^8 2.2×10^5 8.6×10^{11}

considerably higher reactivity. The initial higher reactivity in the bullvalene related systems is due to the larger ring size which allows easier flattening at the bridgehead during ionization.

De Meijere and coworkers[211] have also studied a number of other mono- and dicyclopropyl-substituted bicyclo[2.2.2]octane derivatives to compare with the results of their trihomobarrelene data. The relative rates below are for solvolysis in 80% aqueous ethanol at 25°C. It is interesting to note here that the rate increases for substituting the

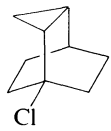
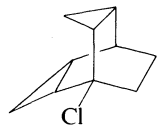
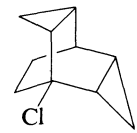
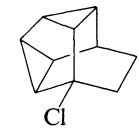






Rel. rates 1.0 2.9×10^4 2.8×10^6 2.8×10^8

second and third cyclopropyls appear to be additive. However, this appears to be a function of the specific system involved as shown by the additional comparison below, also in 80% aqueous ethanol.

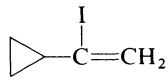





Rel. rates	1.0	96	0.55	0.011

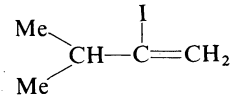
K. Vinyl Cyclopropylcarbinyl Systems

1. Cyclopropylvinyl

In 1969 Sherrod and Bergman[212] and Bässler and Hanack[213] independently reported that cyclopropyl groups strongly stabilize adjacent vinyl cations generated by solvolysis. Thus, 1-cyclopropylvinyl iodide (**105**) reacted with silver acetate in acetic acid at room temperature at a rate which is about 10^3 times faster than that of the corresponding 1-isopropylvinyl iodide (**106**).

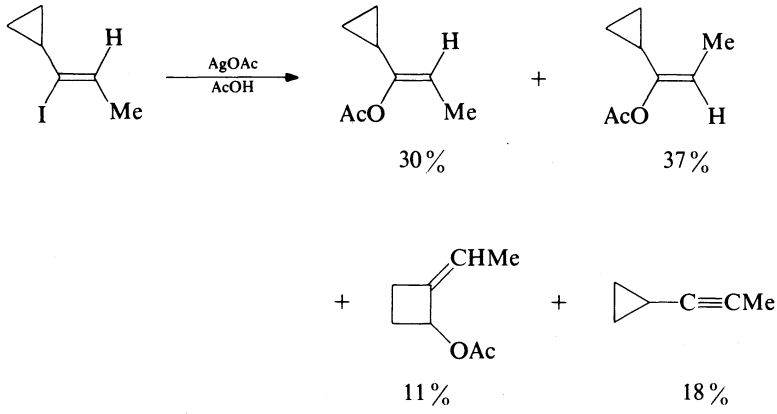


(**105**)

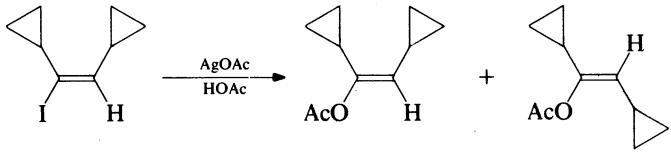


(**106**)

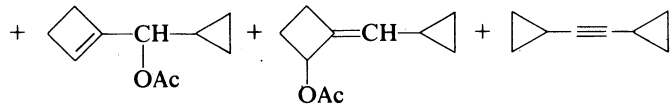
The area of cyclopropylvinyl cation chemistry has been recently reviewed in detail by Stang and coworkers[214] and thus will only be summarized here. The majority of the studies subsequent to the initial report have concentrated on effects of the nature and of the stereochemistry of substituents on the double bond or on the cyclopropane ring on the rates of solvolysis and product ratios[215–220]. A typical example of the product forming-behavior from a cyclopropylvinyl system is given below[217].



Of special interest to the present review is a study by Kelsey and Bergman[221] where the cyclopropylvinyl system contained a β-cyclopropyl substituent. In this system the β-cyclopropyl-substituted compounds were on the average only half as reactive as the corresponding methyl-substituted compounds.



E or *Z* 26% 18%



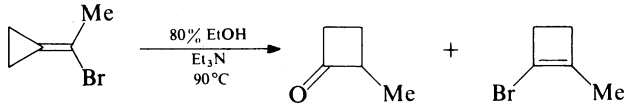
29% 15% 10%

2. *Cyclopropylidenemethyl*

Cyclopropylidenemethyl systems, in which one carbon of the double bond is already part of the cyclopropane ring, give especially stable vinyl cations owing to favorable geometry for overlap with participating cyclopropyl orbitals. This subject has also been reviewed recently in detail[214] and thus will only be summarized here briefly.

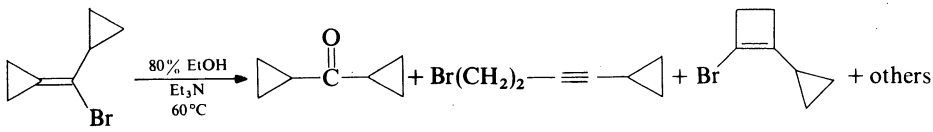
The first report of the solvolysis of a cyclopropylidenemethyl derivative was in 1970 by Ghenciulescu and Hanack[222]. This and other studies[223–229] have supported the involvement of a vinyl cation in the solvolyses of cyclopropylidenemethyl systems.

Typical product-forming behavior for solvolyses of cyclopropylidenemethyl derivatives is that below. The 1-bromo-2-methylcyclobutene results from ion-pair return.



35% 65%

Of special interest for the present review is the study of the solvolysis of the α-cyclopropyl-substituted cyclopropylidenemethyl bromide **107**[230,231]. This system, which is 10^5 times more reactive than the corresponding system without the α-cyclopropyl group and 10^2 times more reactive than the corresponding α-phenyl-substituted system, afforded on solvolysis in 80% ethanol, dicyclopropyl ketone as the major product.



(107) 65% 11% 7% 17%

IV. SYSTEMS HAVING REMOTE CYCLOPROPYL SUBSTITUENTS

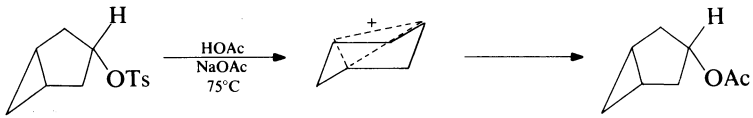
A. Introduction

Owing to the success which investigators have had in finding interesting new kinetic and product-forming behaviors in solvolyses of compounds bearing cyclopropyl substituents α or β to potential cationic centers, it is not surprising that considerable work has also been done with more remote cyclopropyl substituents. In many of the areas which were examined the results have been disappointing. However, in several of the areas entire new fields for study were opened up.

Several general reviews[232,233] on the topic of long-range interactions of cyclopropyl groups with carbocation centers during solvolysis appeared in the mid-1970s. That by Haywood-Farmer[232] is detailed and well organized. The review by Banciu[233], although written in Romanian, is also useful and is not difficult to follow even for the non-reader of Romanian. Because of the existence of these reviews as well as others to be listed later dealing with more specialized areas of remote cyclopropyl participation in solvolyses, this review will attempt in these areas only to summarize the results and update the previous reviews.

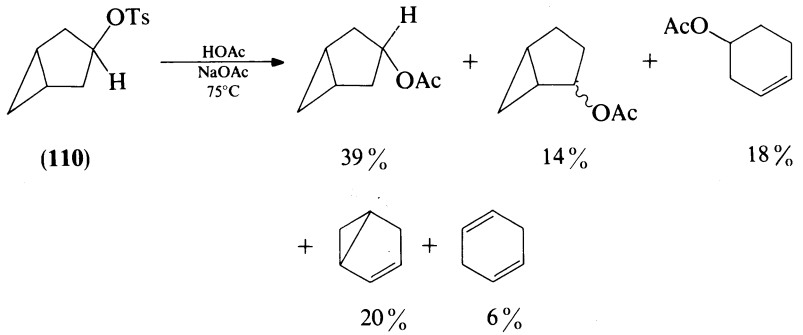
B. 3-Bicyclo[3.1.0]hexyl and Related Systems

The initial report by Winstein and coworkers[234,235] in 1959 that *cis*-3-bicyclo[3.1.0]hexyl tosylate (**108**) undergoes solvolysis with cyclopropyl participation to give a 'homoaromatic' trishomocyclopropenyl cation (**109**), opened up a large new area of



(**108**) (**109**) 99%

remote cyclopropyl chemistry for study. The evidence for this type of cyclopropyl participation has been covered as part of a number of reviews[232,233,236–238] so will not be repeated here in detail. Included among this evidence is the fact that the corresponding *trans* epimer (**110**) does not react with cyclopropyl participation. This is because the backside of its developing p-orbital during ionization is oriented in the wrong direction for overlap with the cyclopropyl orbitals. Thus, it gives a complex product mixture involving solvent displacement as well as hydrogen shifts and alkene formation[236].

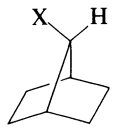
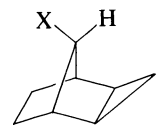
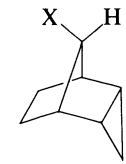


(**110**) 39% 14% 18%

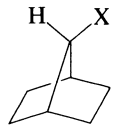
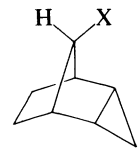
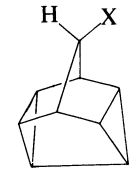
20% 6%

Since the major reviews covering the parent 3-bicyclo[3.1.0]hexyl system appeared in the mid-1970s, several other papers dealing with the system have appeared. In one of these, Mjöberg and coworkers[239] have concluded from analysis of far infrared and microwave data that the bicyclo[3.1.0]hexyl system exists in a boat form in its most stable conformation, and that the chair form in which cyclopropyl participation takes place must be vibrationally highly excited. Also, Walkowicz[240] has reported some further investigations of the influence of alkyl substituents on the chemistry of 3-bicyclo[3.1.0]hexyl tosylates.

The proposal that cyclopropyl participation in solvolysis of the *cis*-3-bicyclo[3.1.0]hexyl tosylate (**108**) proceeds via a trishomocyclopropenyl cation intermediate (**109**) has been firmly established by product, deuterium scrambling and salt effect studies[236]. However, because the cyclopropyl participation in this system requires an unfavorable conformation, it is not apparent from simple kinetic studies. Thus, the *cis*-3-bicyclo[3.1.0]hexyl tosylate (**108**) has an acetolysis rate which is only nine times faster than that of the non-participating *trans* isomer, **110**. However, when the 3-bicyclo[3.1.0]hexyl moiety is incorporated into a tricyclic or tetracyclic structure which locks it into a chair form, dramatically large rate enhancements are found. Some examples from the literature which are provided in the review by Haywood-Farmer[232,241,242] are given below. These

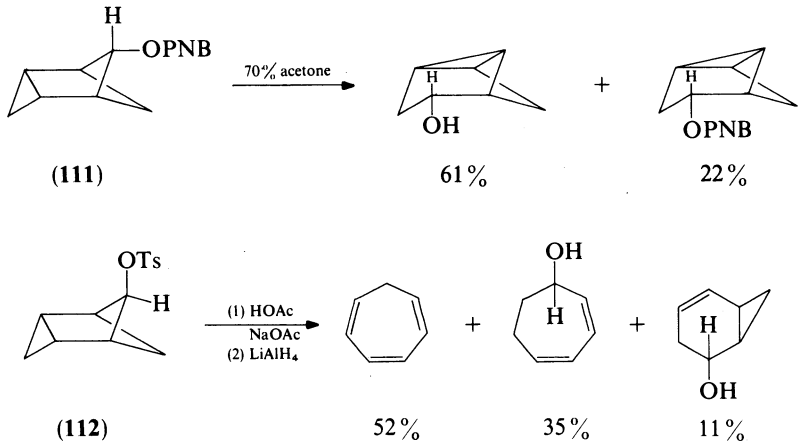
Rel. rates 1.0 1.7 10^{12}

10^4 37 10^{10}

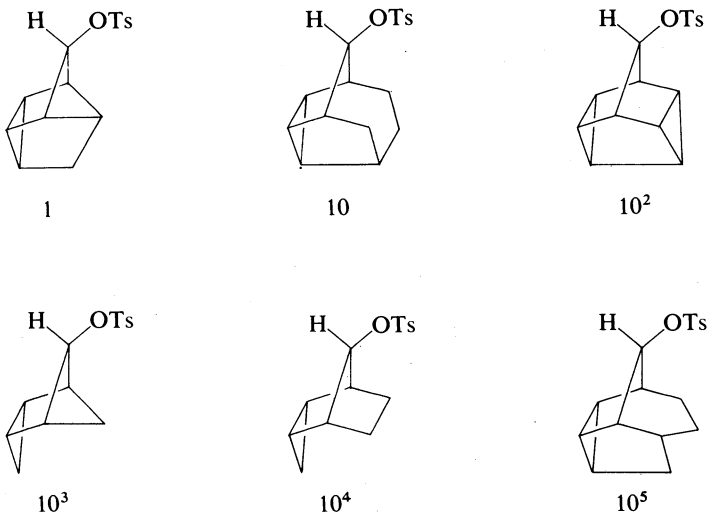
are for brosylates in acetic acid or *p*-nitrobenzoates in 70% dioxane at 100 °C. It is obvious, as was seen in the parent 3-bicyclo[3.1.0]hexyl system that the orientation of the cyclopropane ring and leaving group are critical.

Since the publication of Haywood-Farmer's comprehensive review[232] which covered the literature in detail up through 1972 and in part into 1973, the solvolyses of a number of additional cyclopropane-containing systems have been studied in which trishomocyclopropenyl cations were implicated or discussed. Thus, Masamune and coworkers[243] and Gassman and Creary[244] studied the solvolyses of the *exo*- and *endo-anti*-tricyclo[3.1.1.$0^{2,4}$]heptan-6-yl *p*-nitrobenzoate and tosylate (**111** and **112**) (Scheme 16). For these two compounds, the *exo:endo* rate ratio after correcting for different leaving groups and solvents was 56:1. From looking at the products and from consideration of the relative rates of the non-cyclopropanated materials ($k_{exo}/k_{endo} = 10^{-8}$) it was proposed that a trishomocyclopropenyl intermediate was involved in reactions of the *exo* system **111**.

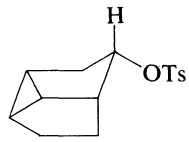


SCHEME 16. Solvolysis products from the *exo-* and *endo-anti*-tricyclo[3.1.1.$0^{2,4}$] heptan-6-yl *p*-nitrobenzoate and tosylate[243,244]

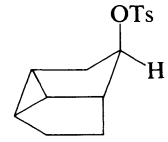
Ellen and Klump[245] have examined several tetracyclic systems containing the 3-bicyclo[3.1.0]hexyl moiety and have reported the following series of relative reactivities which nicely illustrates the large effects of structural changes on the reactions. Those shown here are related to angle strain at the carbon bearing the leaving group.



In a study by Buckeridge and coworkers[246] the solvolyses of the epimeric tricyclic tosylates **113** and **114** shown below were examined. Hydrolysis of the '*cis*' tosylate **113** gave only alcohol of retained structure. Hydrolysis of the corresponding '*trans*' tosylate **114** on the other hand proceeded slowly and yielded a complex mixture of products.

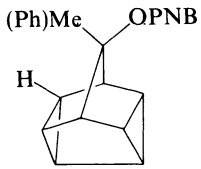


(113)

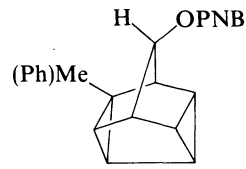


(114)

Coates and Fretz[247] have investigated some substituent effects on their 9-pentacyclononyl system and found results which support a trishomocyclopropenium ion intermediate. Solvolysis of either the tertiary or secondary methyl-substituted *p*-nitrobenzoates **115** or **116** in 65 % acetone at 100 °C furnished the same 80 : 20 mixture of tertiary and secondary alcohols. Similarly, both phenyl-substituted *p*-nitrobenzoates gave a 94 : 6 mixture of tertiary to secondary alcohols. Also, the methyl and phenyl substituent effects on **115** are very much lower than those observed for the corresponding 7-norbornyl system (10^8 and 10^{13}, respectively) indicating a stabilized, delocalized intermediate for the reaction of **115**.



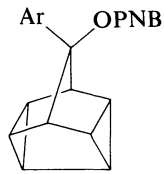
(115)



(116)

k_{Me}/k_H	112	4.8
k_{Ph}/k_H	1600	0.04

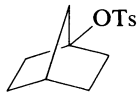
Brown and Ravindranathan[248] have carried out a $\rho\sigma$ study for aryl groups at C(9) of Coates'[247] system (**117**) are shown below. An excellent correlation versus σ^+ was obtained



(117)

with $\rho^+ = -2.05$. For the corresponding 7-aryl-7-norbornyl *p*-nitrobenzoates, ρ^+ was -5.27. This supports the proposal of cyclopropyl participation in the solvolysis.

Chenier and coworkers[249] have studied the acetolysis of 4-nortricyclyl tosylate (**119**) and found it to be 10^5 slower than the bridgehead norbornyl tosylate (**118**). They argue that a substantial portion of the bridgehead reactivity difference is due to inductive electron withdrawal by the cyclopropane ring.

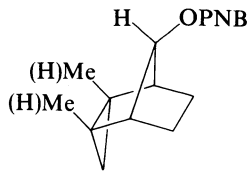


(118)

(119)

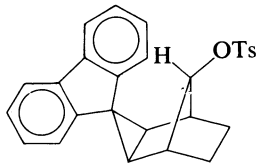
Rel. rates	10^5	1.0

Gassman and coworkers[250] have observed small cumulative methyl substituent effects (accelerations of 2.2 and 4.7 for the first and second methyls, respectively) in the tricyclo[3.2.1.$0^{2,4}$]octyl system **120** which are consistent with a highly delocalized ion.

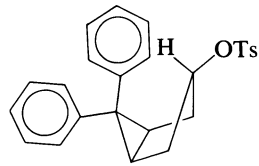


(120)

Wilt and coworkers[251] have made further studies of aryl participation in solvolysis of the *trans*-3-bicyclo[3.1.0]hexyl systems **121** and **122**. Neither underwent significant long-range aryl migration.

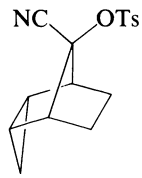


(121)



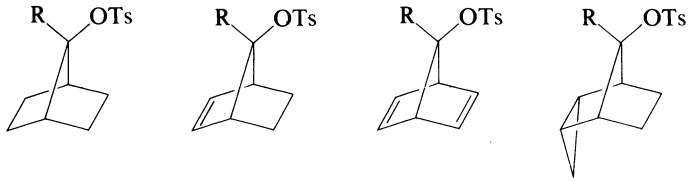
(122)

Finally, Gassman and Talley[252] studied the effects of α-cyano substitution on the kinetics of solvolysis in 2,2,2-trifluoroethanol of the 8-tricyclo[3.2.1.$0^{2,4}$]octyl system **123**.



(123)

The magnitude of the k_H/k_{CN} ratio suggests that in this system the charge is so effectively delocalized that both the inductive and conjugative contributions of the α-cyano group decrease significantly.



Rel. rates	R = H	1	10^{11}	10^{14}	10^{14}
	R = CN	10^{-2}	10^{6}	10^{8}	10^{10}

C. Other 2-Cyclopropylethyl Systems

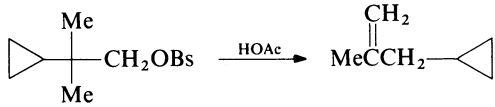
Because of the observation that cyclopropyl participation is of major importance in the solvolysis of 3-bicyclo[3.1.0]hexyl and related systems, a large number of investigations looking for evidence of cyclopropyl participation in other cyclopropylethyl systems have also been carried out. Most of the earlier work in this area has already been covered in detail in the reviews by Haywood-Farmer[232], Banciu[233] and Barkhash[238]. Thus, for the present review, the earlier work will just be summarized and any new information presented.

1. Primary 2-cyclopropylethyl

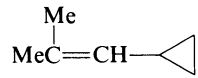
In more nucleophilic solvents, cyclopropyl participation in solvolysis of simple 2-cyclopropylethyl systems such as **124** is weak compared to solvent participation[253, 254].

(**124**)

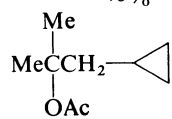
However, in the good ionizing but only weakly nucleophilic solvent 2,2,2-trifluoroethanol (TFE), Rhodes and coworkers[255] found kinetic as well as product evidence (Scheme 17) that the β-cyclopropyl group does indeed participate to a small extent. Also, Rhodes and Takino[256] have demonstrated cyclopropyl participation in a sterically hindered neopentyl type system (**125**).



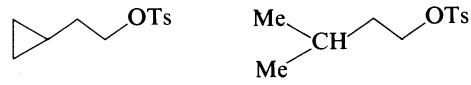
(**125**) 21%



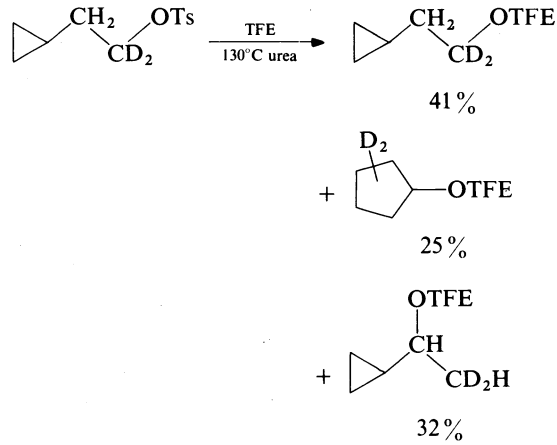
40%



35%

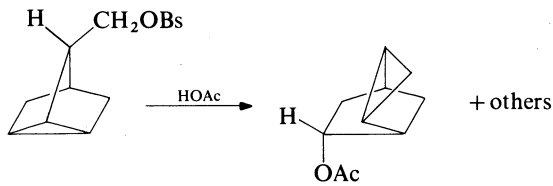


Rel. rates 75 °C	TFE	3.3	1.0
	EtOH	0.92	1.0



SCHEME 17. Relative rates and products of trifluoroethanolysis of 2-cyclopropylethyl tosylate[255]

Nortricyclyl-3-carbinyl tosylate (**126**) has been investigated by several groups[232] and found to give products which could involve cyclopropyl participation.

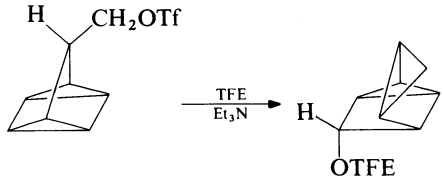


(**126**)

Gassman and coworkers[257] have studied possible cyclopropyl participation in the bicyclo[2.1.0]-2-carbinyl tosylate systems **127** and **128**. However, the products were explained in terms of cyclobutane ring bond shifts.

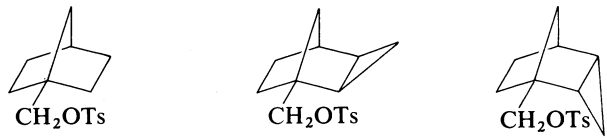
(**127**) (**128**)

Dauben and Vinson[258] examined the trifluoroethanolysis of quadricyclyl-7-carbinyl triflate (**129**) and obtained a high yield of cyclopropyl-participated product.

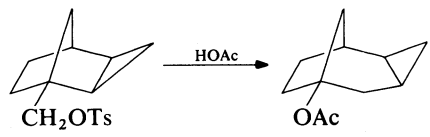


(**129**) 80%

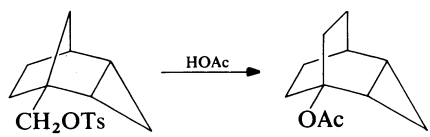
Recently, Chenier and coworkers[259] have reported long-range cyclopropyl participation in acetolyses of '*exo*'-tricyclo[3.2.1.$0^{2,4}$]octyl-1-carbinyl tosylate (**130**) (Scheme 18). The reaction of the corresponding '*endo*' isomer, **131**, however, does not appear to take place with any cyclopropyl involvement.



Rel. rates 25 °C 1.0 6.5 0.87



(**130**) > 95%

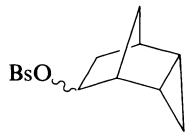


(**131**) > 99%

SCHEME 18. Relative rates and products of acetolysis of *exo*- and *endo*-tricyclo[3.2.1.$0^{2,4}$]octyl-1-carbinyl tosylate[260]

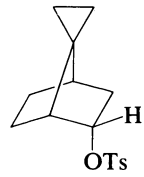
2. *Norbornyl related*

This area has been reviewed in detail by Haywood-Farmer[232] and no major new literature reports on the subject have appeared. There is kinetic evidence that some cyclopropyl participation does occur in 5,6-cyclopropyl-fused *exo*-norbornyl and related type systems where the cyclopropane is also *exo*[260]. This is seen in the *exo*/*endo* rate ratio of 1130 for acetolysis of the *exo*-cyclopropyl isomer shown below. The *exo*/*endo* rate ratio of 385 for the *endo*-cyclopropyl isomer is almost identical to that of 350 for the



$k_{exo/endo}$ HOAc, 25°C	1130	385

unsubstituted 2-norbornyl brosylate. However, the magnitudes of the kinetic effects are not large. 7-Spirocyclopropyl participation in solvolysis of the norbornyl derivative (**132**) has not been found to be effective[126].

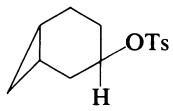


(132)

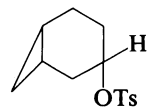
3. Bicyclo[n.1.0] related

The solvolyses of several bicyclo[n.1.0]alkan-3-yl systems larger than [3.1.0] have been investigated for evidence of cyclopropyl participation. Although product studies have revealed interactions of the cyclopropanes in certain of these cases with the cationic center, it is not clear from the kinetic results whether the participation is also involved in the rate-determining ionization or just in a subsequent step.

Hanack and Krause[261] have studied the acetolyses of the 3-bicyclo[4.1.0]heptyl tosylates (**133** and **134**). Although rate enhancements of 37 and 53 relative to cyclohexyl



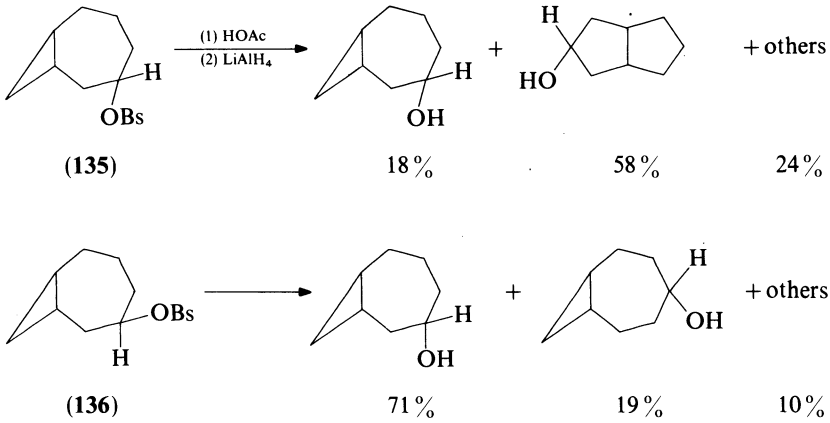
(133)



(134)

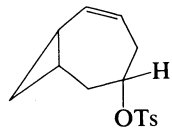
tosylate were seen for **133** and **134**, respectively, product and deuterium labeling studies rule out any cyclopropane participation.

Cope and coworkers[262] carried out a product study on acetolysis of the epimeric 3-bicyclo[5.1.0]octyl brosylates (**135** and **136**) (Scheme 19). However, no kinetics were measured. Formation of the bicyclo[3.3.1]octan-3-yl product from the *endo* brosylate (**135**) reveals that some cyclopropyl participation may be involved.



SCHEME 19 Products of acetolysis of epimeric 3-bicyclo[5.1.0]octyl brosylates[262]

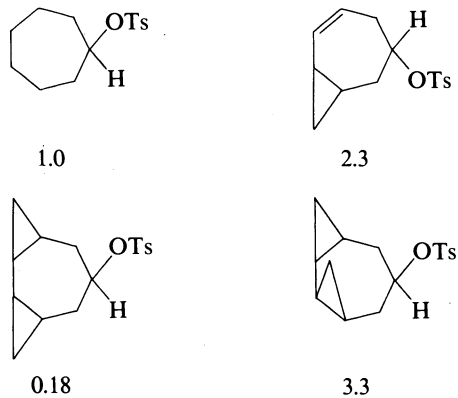
Lambert and coworkers[263, 264] have studied the competition for participation between a double bond and a cylopropane ring in a bicyclo[5.1.0]hex-5-en-3-yl tosylate (**137**).



(**137**)

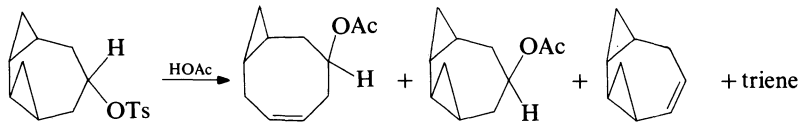
A detailed analysis of the products led the investigators to conclude that approximately 80% of the reaction occurred by double-bond participation and 20% by cyclopropyl participation.

Paquette and Detty[265, 266] have examined the acetolyses of several biscyclopropylethyl systems contained in a seven-membered ring. Some relative rate data are as follows. From



analysis of kinetics, products and deuterium labeling results, the authors concluded that interaction of one *cis*-oriented cyclopropyl group in each of the biscyclopropyl compounds is minimally indicated. However, more extended interactions of both cyclopropane rings could not be supported with the data available.

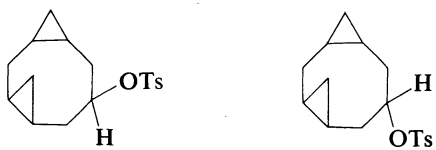
In the course of the same work Paquette and Detty[265] also studied an additional isomeric biscyclopropyl-substituted cycloheptyl tosylate (**138**). The products, however,



(138) 55% 9% 25% 11%

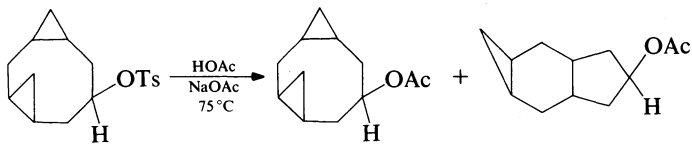
were complex and the formation of large amounts of alkene products is inconsistent with cyclopropyl participation.

Winstein and coworkers[267] investigated the epimeric biscyclopropylethyl moiety containing cyclooctyl tosylates **139** and **140**. The all-*cis* tosylate **139** underwent acetolysis



(139) **(140)**

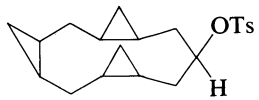
about 50 times faster than its *trans* epimer **140**, but about 60 times slower than cyclooctyl tosylate. The major products from the all-*cis* tosylate **139**, the kinetic results and deuterium labeling results require an interaction of one of the cyclopropane rings with the



(139) 73% 18%

cationic center generated in the transition state. However, they do not support a more extensive interaction of both cyclopropyl groups to a pentahomocyclopentadienyl cation type intermediate or, in fact, to a trishomocyclopropenyl type cation as shown in the paper.

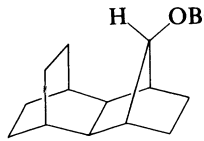
Winstein and coworkers[268] have also investigated cyclopropyl participation in the tosylate **141** below. However, the rates, products (97% elimination) and deuterium scrambling results indicate the lack of major amounts of any cyclopropyl participation.



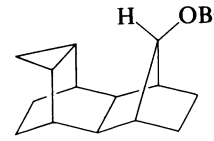
(141)

D. More Remote Cyclopropyl-substituted Systems

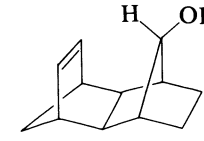
In a few cases with rigid molecules, participation in solvolyses by cyclopropane rings which are quite remote from the carbocation center have been observed. One of the most pronounced, as judged by rate data, is with compound **143** shown below[269]. The relative



(142)



(143)

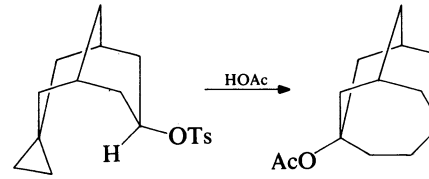


(144)

Rel. rates	1	10^5	10^7

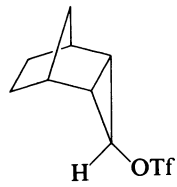
rates of **142–144** are for acetolysis at 25 °C. However, as has been pointed out by Haywood-Farmer in his review[232], owing to the fact that the cyclopropyl participation in **143** is less than the double-bond participation in **144**, and the product mixture is complex, the precise nature of the cyclopropyl effect is unclear.

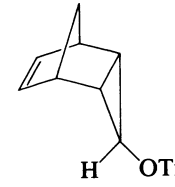
Another system where long distance cyclopropyl participation seems to be occurring is in the spiro tosylate **145** shown below[270] which forms homoadamantyl acetate (**146**) as the only product and also is 5000 times more reactive than cyclohexyl tosylate.

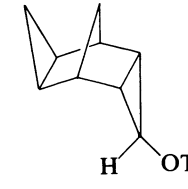


(145) (146)

Creary[271] has reported long distance cyclopropyl participation in acetolysis of *endo*, *exo*-tetracyclo[3.3.1.$0^{2,4}$.$0^{6,8}$]non-*exo*-3-yl triflate (**147**). Hydrolysis in 65% aqueous

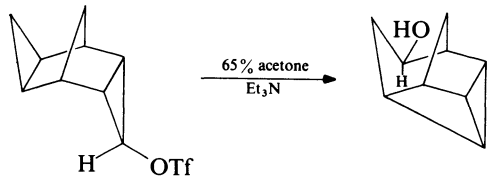






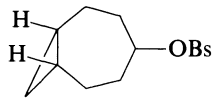
Rel. rates	1.0	81	7.1

acetone gave four products in unspecified amounts with the structure of the major one being as shown.

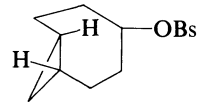


(147)

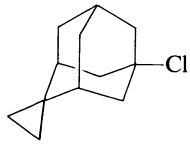
A number of systems which did not undergo remote cyclopropyl participation are summarized in Haywood-Farmer's review[232]. The structures of some of these are given in Scheme 20 together with those for several more recently studied systems.



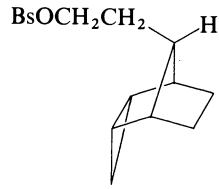
Ref. 262



Refs 272, 273



Ref. 274



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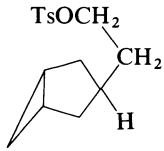
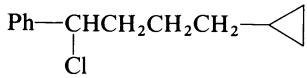


Refs 276, 277

Ref. 249



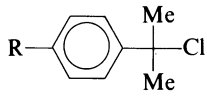
Ref. 278

SCHEME 20 Several systems in which remote cyclopropyl participation is absent

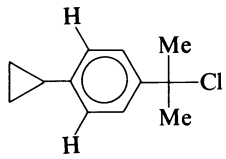
E. Systems having Remote Cyclopropyl Substituents which are Delocalized through Intervening π-Bonds

One of the simplest arrangements in which cyclopropyl substituents have the possibility of interacting with a carbocation center through connecting π bonds is for the case of aryl

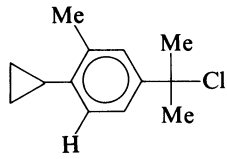
ring cyclopropyl-substituted benzyl systems. Some rate results from Brown and Cleveland[279] which illustrate the relative importance of cyclopropyl substitution in the hydrolysis of *t*-cumyl chlorides in 80% aqueous acetone at 25 °C are given below. The



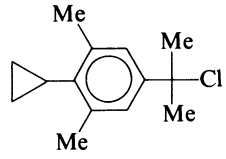
R =	H	Me	Ph	*i*-Pr	*c*-Pr
Rel. rates	1.0	26	7.7	18	154



Rel. rates 154

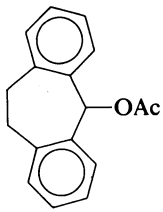


169

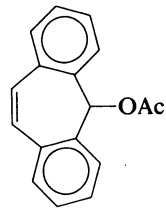


36

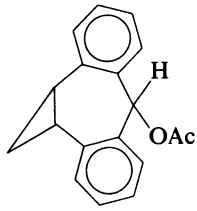
effects of added 3,5-substituents show that the cyclopropyl group prefers a bisected conformation for electron release. Some other examples of cyclopropyl assistance to solvolysis through benzene rings are given in Scheme 21[280–283].



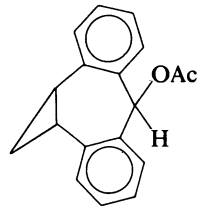
Rel. rates 1.0



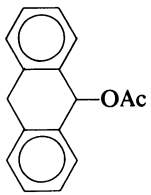
350



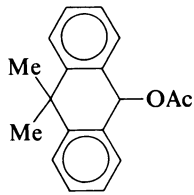
2.0



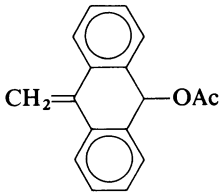
0.0083



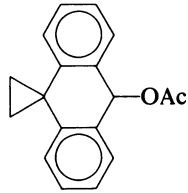
Rel. rates 1



1



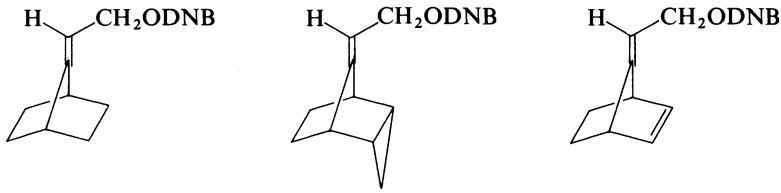
1



100

SCHEME 21 Relative rates for some systems in which cyclopropyl assistance to solvolysis through benzene rings has been studied[280–283]

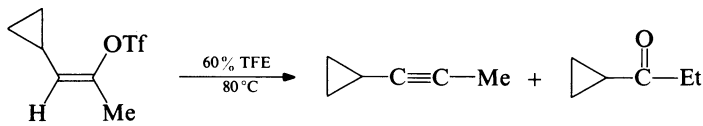
Cyclopropanes can also react with carbocation centers through carbon–carbon double bonds. One example, **148**, has been reported by Sargent and Herkenham[284].



(148)

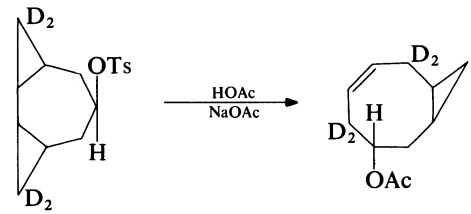
Rel. rates 70% acetone 100°C	1.0	620	26

In solvolysis of 3-cyclopropyl-2-propen-2-yl triflate (**149**) in aqueous trifluoroethanol at 80°C, the stabilizing influence of the β-cyclopropane ring promotes 1,2-hydride shift across the double bond[285].

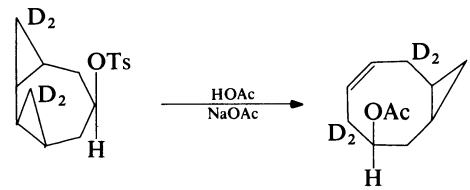


(149) 81% 12%

Finally, in the course of their solvolytic study of the bishomocycloheptadienyl tosylates **150** and **151**, Paquette and Detty[265] made an interesting observation of a cyclopropyl through cyclopropyl interaction.



(150)



(151)

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CHAPTER **12**

Cyclopropyl radicals, anion radicals and anions

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I. GENERAL INTRODUCTION

This chapter deals with some of the reactive intermediates of cyclopropanes—radicals, anion radicals and anions. It is hoped that the reader will appreciate that the cyclopropane ring, because of its unique bonding, affords one with a tool to study the mechanism of a variety of reactions. The mechanism of many of these reactions will be discussed in some detail in this chapter. It should also be noted that whenever possible stereochemistry has been used as a mechanistic probe. Pertinent literature has been reviewed through most of 1985.

II. CYCLOPROPYL RADICAL[1]

A. Structure

The valence bond description, originating with Förster[2] and refined by Coulson and Moffitt[3], provides a useful model of the bonding in cyclopropane. In this approach two sets of hybridized orbitals are used, one set for the *endo* bonds and the other set for the *exo* bonds. The orbitals associated with the *endo* bonds are calculated to be $sp^{4.12}$ hybridized and those associated with the *exo* bonds $sp^{2.28}$ hybridized. This hybridization corresponds to a bond angle of 104° for the *endo* orbitals and 116° for the *exo* orbitals (Figure 1).

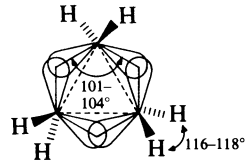

FIGURE 1. *Exo* and *endo* bonds in cyclopropane
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A refinement[3] of Coulson's and Moffitt's calculation suggests hybridization of the *endo* orbitals as sp^5 with a bond angle of 101° 32′ and the *exo* orbitals as $sp^{2.28}$ with a bond angle of 116°. The greater p character of the *endo* bonds and the greater s character associated with the *exo* bonds accounts for most of the physical and chemical properties of the cyclopropane[4, 5]. The molecule is highly strained with an estimated strain energy of 27.6 kcal mol^{-1} or 9.2 kcal mol^{-1} per CH_2 group. The strain is largely a result of bond angle distortion (Baeyer strain) and non-bonded repulsions (Pitzer strain)[6].

Converting cyclopropane to a planar cyclopropyl radical (Figure 2) would result in the relief of Pitzer strain (four H–H interactions), but would at the same time increase bond angle distortion (104°–120°), thereby causing greater internal (I)-strain[7].

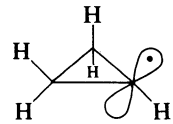


FIGURE 2. Planar cyclopropyl radical

This latter effect may be one of the reasons for the observation that the cyclopropyl radical, in contrast to other cyclic and acyclic radicals, exists as a bent radical[8, *] Delocalizing substituents (X = π-systems) attached to the radical site could convert the cyclopropyl σ radical to a π radical. On the other hand electronegative substituents (i.e. oxygen and fluorine) attached to a radical site have a tendency to convert what would ordinarily be a π radical to a σ radical[8]. Such substituents attached to the cyclopropyl radical site could reinforce the σ character of the radical and thereby decrease the rate of inversion. Unless constrained, for example at a bridgehead, a σ radical such as cyclopropyl would rapidly invert its configuration ($k_1 \simeq 10^8\ s^{-1}$ at $-175\,°C$), with the inversion proceeding through a π radical transition state (Figure 3).

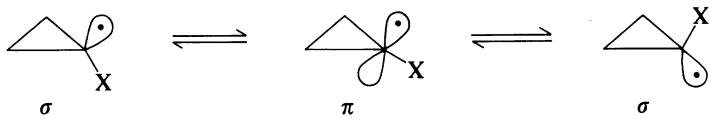


FIGURE 3. Inversion via planar transition state

Hoffmann-type extended Hückel theory (EHT) calculations[9] have been carried out on the parent cyclopropyl radical[10]. The calculations were in reasonable agreement with the ESR spectral results obtained by Fessenden and Schuler[8]. However, the predicted α-

* The term σ radical is applied to those radicals in which the electron occupies an hybridized orbital and a π radical to those in which the electron occupies a p orbital.

proton coupling constant of 24.89 Gauss was in poor agreement with the observed value of 6.51 Gauss. The inversion barrier for flipping from one σ to another was calculated to be 0.5 kcal mol^{-1} and the out-of-plane angle for the α-CH bond was estimated to be 20°.

INDO calculations by Kochi and coworkers[11] gave an out-of-plane angle for the α-CH bond of 35° with an inversion barrier of 3.2 kcal mol^{-1}. The calculated coupling constants for the *syn* and *anti* β-protons are nearly equal to each other for all values of the bonding angle, which would indicate that this datum cannot necessarily be used as evidence for a rapidly inverting σ radical.

Ab initio Hartree–Fock (HF) calculations of the structure of the cyclopropyl radical by Dupuis and Pacansky[12] also showed that the α-CH bond is bent with an out-of-plane α-CH angle of 39.3° with an inversion barrier of 3.0 kcal mol^{-1}. Moreover, compared to cyclopropane itself, the α-CH bond is slightly shorter and the C–C bonds are no longer equivalent. The α-CC bond lengths are shorter (1.476 Å vs. 1.501 Å) and the β-CC bond length is longer (1.54 Å). This means that the σ radical causes the strengthening of the α-CC bonds and the weakening of the β-CC bond. This result is consistent with the observed mode of rearrangement of the cyclopropyl radical to the allyl radical (*vide infra*).

In addition the HF calculations show that no significant hyperconjugative interaction takes place between the σ radical center and the β-CH bonds. This view is contradicted by the ESR results of Kawamura and coworkers[39] who conclude from their data that the σ-cyclopropyl radical is hyperconjugatively coupled with the β-CH bonds and that the coupling is stronger with the *cis* bond than with the *trans* bond.

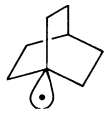
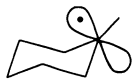
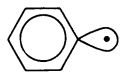
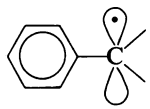
The heat of formation $(\Delta H_f^0)_{298}$ of the cyclopropyl radical has been determined[13] experimentally to be 66.9 ± 0.25 kcal mol^{-1}, and the C–H bond dissociation energy for the cyclopropyl carbon–hydrogen bond in cyclopropane was found to be 106.3 ± 0.25 kcal mol^{-1}. This bond dissociation energy is less than the C–H bond dissociation energy in ethylene (108 kcal mol^{-1}) and in benzene (110 kcal mol^{-1}) and is a reflection of hybridization ($sp^{2.28}$) of the exocyclic bonds in cyclopropane. The above data were obtained from the bimolecular rate constant for the reaction of chlorine atoms with cyclopropane to give hydrogen chloride and the cyclopropyl radical. Ion cyclotron double resonance spectroscopy[14] was in complete agreement giving $(\Delta H_f^0)_{298} = 66.6 \pm 0.1$ kcal mol^{-1} and a bond dissociation energy of 105.9 ± 2.2 kcal mol^{-1} for the cyclopropyl carbon–hydrogen bond, and a value of 111.1 ± 2.2 kcal mol^{-1} for the C–H bond in ethylene.

In general, σ radicals, such as cyclopropyl, are more electrophilic than π radicals[15]. The larger the s character of an orbital, the greater the electronegativity of that orbital and the greater is its electrophilic character (less nucleophilic).

B. Reactivity

Consistent with the σ nature of the cyclopropyl radical is its reactivity. In general, σ radicals are more reactive and less selective than π radicals. It has been found for example, that phenyl, vinyl and cyclopropyl σ radicals will abstract hydrogen atoms from saturated hydrocarbons at 77 K, conditions under which π radicals are unreactive[15]. From Rüchardt's[16] radical reactivity data (Table 1), one notes that the bridgehead 1-bicyclo[2.2.2]octyl radical, which should be a standard for σ radicals since it cannot invert its configuration, is the least selective. The benzyl radical, a delocalized radical, is the most selective. The cyclohexyl radical, a non-delocalized π radical, is intermediate in selectivity. The phenyl radical, a non-inverting σ radical in an sp^2 hybridized orbital shows greater selectivity than a non-inverting σ radical in an sp^3 hybridized orbital. The cyclopropyl radical, an inverting σ radical in an $sp^{2.28}$ hybridized orbital, most nearly resembles the non-inverting phenyl σ radical but is more selective and less reactive. The advantage of

TABLE 1. Competition constant r for the reaction of R$^{\cdot}$ with $BrCCl_3$ and CCl_4[16]

R$^{\cdot}$	Type	T(°C)	r^a
	σ	80	59
	π	11	566
	σ	110	278
	σ	104	184
	π	80	1700

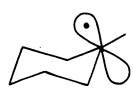
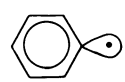
[a] $r = k_{Br}/k_{Cl}$.

Rüchardt's experiments is that they minimize polar effects in the reaction of the radicals since the same leaving group, the $\cdot CCl_3$ radical, is involved in both radical abstraction reactions.

$$\cdot CCl_3 + R\text{-}Br \underset{k_{Br}}{\overset{BrCCl_3}{\rightleftarrows}} R\cdot \xrightarrow[k_{Cl}]{CCl_4} R\text{-}Cl + \cdot CCl_3$$

From the relative reactivity data, shown in Table 2, which describes the thermal decomposition of biscyclopropanoyl peroxide in a series of substituted benzenes, Shono and Nishiguchi[17] have concluded that the cyclopropyl radical more closely resembles the

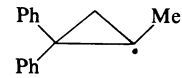
TABLE 2. Relative reactivity in homolytic aromatic substitution[17]

Aromatic			
PhCl	3.5	1.1	1.78
PhOMe	2.3	1.7	1.95
PhCN	2.7	3.7	3.59
PhMe	0.76	1.2	1.03
PhBu-*t*	0.28	0.64	0.59

phenyl[18] σ radical in its reactivity than it does the cyclohexyl[19] π radical. The 2-phenylcyclopropyl radical behaves similarly to the cyclopropyl radical[17].

In its relative reactivity toward toluene, ethylbenzene and cumene the more highly substituted 1-methyl-2,2-diphenylcyclopropyl radical[20], derived from the decomposition of the precursor diacyl peroxide, resembles the chlorine radical more than it does the phenyl radical (Table 3). Similarly, comparison of the relative reactivities of primary, secondary and tertiary aliphatic hydrogens toward chlorine atoms (1.0:3.6:4.2)[21] and phenyl radicals (1.0:9.3:44)[21] with the relative reactivities of the C–H bond in the methanol/ethanol/2-propanol series toward the 1-methyl-2,2-diphenylcyclopropyl radical (1.0:2.4:3.5)[20] further confirms the low selectivity of the cyclopropyl radical. Again, this radical resembles the chlorine atom in its reactivity more than it does the phenyl radical.

TABLE 3. Relative reactivities (per hydrogen) of hydrogen donors toward a variety of radicals[20]

R–H/Radical	$Br^{\bullet}$	$Me^{\bullet}$	$Ph^{\bullet}$	$Cl^{\bullet}$	
	40°	65°	60°	40°	65°
Toluene	1	1	1	1	1
Ethylbenzene	17.2	4.1	4.6	2.5	1.8
Cumene	37.0	12.9	9.7	5.5	2.5

In so far as the rate of formation of radicals reflects their stability or reactivity the findings of Hart and Wyman[22] are instructive. In carbon tetrachloride the rate of decomposition of benzoyl peroxide was twice as fast as that of biscyclopropanoyl peroxide. Ingold and coworkers[23] have found that in the photodecomposition of benzoyl and biscyclopropanoyl peroxides, in carbon tetrachloride at 298 K, the phenyl radicals produced reacted faster ($7.8 \times 10^6\ M^{-1}\ s^{-1}$) than the cyclopropyl radicals ($1.5 \times 10^6\ M^{-1}\ s^{-1}$). These results are consistent with C–H bond dissociation energies for benzene (110 kcal mol) and cyclopropane (106 kcal mol^{-1}) which implies that the cyclopropyl radical should be less reactive than the phenyl radical. In subsequent work[23b] they also showed that at ambient temperatures radical reactivities decreased along the series: $k = Ph^{\bullet} > (Me)_2C{=}CH^{\bullet} >$ cyclopropyl$^{\bullet} > Me^{\bullet}$. Table 4 records the absolute rate constants for the reaction of these radicals with tri-*n*-butylgermane.

Other findings which show the difficulty in forming the cyclopropyl radical by some radical molecule reactions are the failure of chlorine atoms to abstract the tertiary ring hydrogen from methylcyclopropane[24] and the failure of *t*-butoxy radicals[25] to abstract the

TABLE 4. Absolute rate constants for reactions of various radicals with tri-*n*-butylgermane[23]

Radical	T(°C)	$10^{-6}\ k, M^{-1}\ s^{-1}$
$Ph^{\bullet}$	29	260 ± 28
$(Me)_2C{=}CH^{\bullet}$	27	35 ± 5
	30	13 ± 2
$Me^{\bullet}$	27	0.5

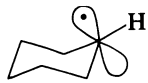
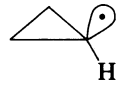
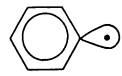
tertiary hydrogen from a variety of alkylcyclopropanes. Hydrogen abstraction from the cyclopropylcarbinyl C atom is, as expected, preferred in these cases. The failure of cyclopropanecarboxaldehyde to undergo decarbonylation reaction with di-*t*-butyl peroxide[26] to yield the cyclopropyl radical is another good example of the difficulty in producing the cyclopropyl radical. However, 1-methyl- and 1-phenylcyclopropanecarboxyaldehyde did decarbonylate to yield methyl- and phenylcyclopropane, respectively. Also, photochemical chlorination[27] and vapor phase nitration[28] of cyclopropane have been reported. The relative reactivity of cyclopropane vs. neopentane toward a variety of radicals is shown in Table 5.

TABLE 5. Relative reactivities of C–H bonds in cyclopropane (c) and neopentane (n) toward radicals

Radical	T(°C)	k_c/k_n
$Cl^{\bullet}_{(g)}$	250	0.03
$Cl^{\bullet}_{(l)}$	68	0.13
$Me^{\bullet}$	182	0.65
$MeO^{\bullet}$	250	0.4
$t\text{-BuO}^{\bullet}$	68	0.2

Of the cycloalkyl radicals, the cyclopropyl radical is the least nucleophilic. This is in keeping with the σ character of cyclopropyl radicals. Table 6 compares the *meta/para* ratios obtained from the reaction of phenyl σ radical, cyclopropyl σ radical and cyclohexyl π radical with substituted benzenes[17]. This demonstrates that cyclopropyl and phenyl σ radicals are less nucleophilic than the cyclohexyl π radical.

TABLE 6. The *meta/para* ratios in radical aromatic substitution of PhX[17]

X			
Cl	2.8	1.9	1.8
OMe	5.6	1.5	1.4
CN	0.09	0.43	0.33
t-Bu	2.5	1.9	1.8

It has also been shown in radical substitution at the 2-position of a series of 4-substituted (CN, MeO, Me) protonated pyridines, that the cyclopropyl radical is the least nucleophilic of the cycloalkyl radicals[29]. This low nucleophilicity is consistent with the observed difficulty[30] in oxidizing the cyclopropyl radical by Cu^{2+}. The lack of reactivity of the 2-phenylcyclopropyl radical, generated by the thermal decomposition of the 2-phenylcyclopropanepercarboxylic acid, towards the O–O peracid bond to yield 2-phenylcyclopropanol is also in line with the radical's weak nucleophilicity[31]. However from a study of relative rates of hydrogen abstraction to olefin addition of the cyclopropyl radical to a variety of olefins (Table 7) Stefani and coworkers[32] concluded that the cyclopropyl radical was decidedly nucleophilic.

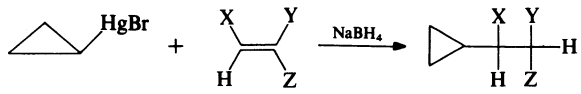
$$R{-}H + S^{\bullet} \underset{k_1}{\overset{S-H}{\rightleftarrows}} R^{\bullet} \overset{k_2}{\rightleftharpoons} R{-}\overset{|}{\underset{|}{C}}{-}\dot{C}\diagup\!\!\diagdown$$

TABLE 7. Relative rate constants for hydrogen abstraction from (k_1) and addition of cyclopropyl radicals (k_2) to olefins at 65°C[32]

Olefin	Mean k_2/k_1	Olefin	Mean k_2/k_1
CH_2=CH_2	23.4	CH_2=CHCl	40.6
E-MeCH=CHMe	5.7	*E*-EtO_2CCH=$CHCO_2Et$	630
$(Me)_2C$=$C(Me)_2$	1.7		

Moreover, cyclopropyl radicals, generated by the $NaBH_4$ reduction of cyclopropylmercuric bromide in the presence of excess olefins possessing one or two electron-withdrawing groups, yielded the addition product in good yields (60%)[33] (Table 8).

TABLE 8. Cyclopropyl radical addition to olefins XCH=CYZ[33]



X	Y	Z	Yield (%)
H	H	CO_2Me	53
H	H	CN	61
H	Cl	CN	61
CO_2Et	H	CO_2 Et	67

In summary, the cyclopropyl radical behaves as a highly reactive and poorly selective rapidly inverting σ radical with a degree of nucleophilicity that has not been firmly established.

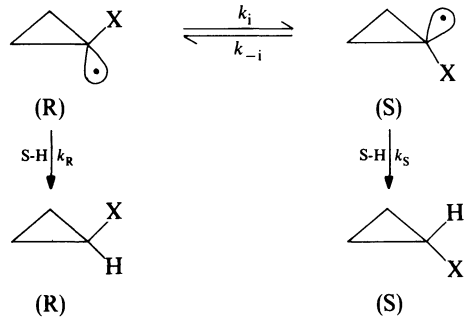
C. Stereochemistry

If the cyclopropyl radical is a rapidly inverting σ radical ($k_i = 10^8\ s^{-1}$ at -175°C and $10^{11}\ s^{-1}$ at 71°C)[8,23b] is there any possibility that such a radical, generated at a chiral center, could maintain its configuration? Obviously for this to happen the radical would have to react, i.e. abstract an hydrogen atom faster than it inverts. Since the inversion frequency ($\sim 10^{11}\ s^{-1}$) is close to that of the diffusion rate ($\sim 10^{11}\ s^{-1}$)[34c] a reaction in which the configuration is maintained must occur at a rate faster than the diffusion of the radical through the solvent. The only hope of observing a chiral radical is either to slow down the inversion frequency (k_i) and/or increase the rate of reaction (k_R, k_S) with the solvent. The former might be accomplished by introducing a substituent X which is capable of decreasing the k_i or by placing the radical on a solid surface with which it can somehow interact. A cage reaction, disproportionation or combination, would also lead to retention of configuration since k_R might be expected to be very close to or greater than k_i (Scheme 1); see also Section II.C.3.

1. *Effect of α-substituents*

a. Theoretical considerations

In general, increasing the s character of the orbital containing the unpaired electron will stabilize the radical and decrease the rate of inversion[9]. Both cyclopropyl and vinyl radicals



SCHEME 1

are bent σ radicals and their inversion barriers are larger than those of their acyclic and saturated counterparts[34a].

Two theories have been advanced to explain why electronegative substituents tend to cause the radical to be a σ radical. Walsh[35a] and Pauling[35b] propose that the effect is due to a difference in electronegativity which would cause the orbital occupied by the odd electron to have a greater amount of s character. Any highly electronegative substituent would therefore enhance the non-planarity of the radical and the substituent effect should parallel the electronegativities of the group. Wells[36] has published a critical review dealing with group electronegativities; a portion of this compilation of mutually consistent group electronegativities is presented in Table 9.

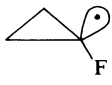
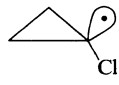
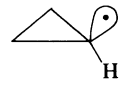
TABLE 9. Mutually consistent group electronegativities[36]

Group	Empirical values	Group	Empirical values
F	3.95	Cl	3.03
MeO	3.70	Br	2.80
H_2N	3.37	Me	2.30
CF_3	3.35	H	2.28

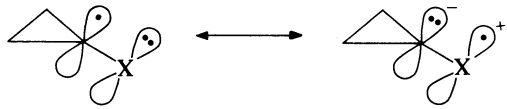
Dewar and Shanshal[34a] argue that the electronegativity of the substituent is not the factor which accounts for the increased configurational stability of the free radicals and that stabilization in the cyclopropyl radical is due to an antibonding interaction between the non-bonding electrons of the substituent and the MOs arising from the interactions between the singly occupied carbon AO and the MOs of the adjacent C bonds. As the result of MINDO/3 calculations it was predicted that the barrier to inversion, caused by a substituent at the radical site, should increase in the order O < Cl < F. This order is at variance with that predicted solely on the basis of group electronegativities which would be Cl < OMe < F. CNDO/2 calculations[37] of inversion barriers of a number of X-substituted cyclopropyl radicals are given in Table 10.

Electronegativity may be a necessary but not a sufficient property to cause a radical to maintain its configuration. As we can see from Table 9 the CF_3 group is highly electronegative yet the geometry of a carbon radical to which it is attached is not much affected by replacing the hydrogens with CF_3 groups[38]. Another important factor is whether or not there is a significant delocalization in the transition state for the inversion process when the σ radical becomes a π radical. When this type of delocalization becomes

TABLE 10. Calculated (CNDO/2) inversion barriers[37]

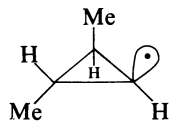
Radical			
Inversion barrier (kcal mol^{-1})	10.5	4.0	0.8

significant then the energy barrier for inversion will be lowered. With second row elements such as N, O and F, contributions from this type of delocalization will be minimal. They will only become significant for higher row elements, i.e. X = S, Cl, Br and I or when X is part of a system such as a carbon in a vinyl, cyano, carbonyl, etc.

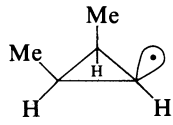


b. Fluorine

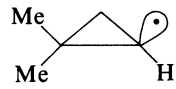
As the most electronegative element, fluorine would be expected to have the greatest effect on the stereochemical stability of the cyclopropyl radical and it does. When comparing ESR spectra of cyclopropyl radicals with 1-fluoro cyclopropyl radicals Kawamura and coworkers[39] found the inversion frequencies of **1**, **2** and **3** at $-99°C$ comparable to that found for the parent cyclopropyl radical, $\sim 10^8\ s^{-1}$ at $-175°C$. In contrast, the inversion frequency of the α-fluorocyclopropyl radicals **4**, **5** and **6** is estimated to be lowered to $10^6\ s^{-1}$ at $-108°C$.



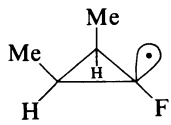
(1)



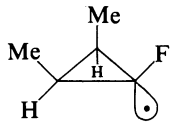
(2)



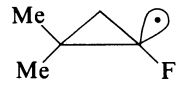
(3)



(4)

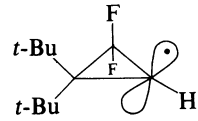


(5)

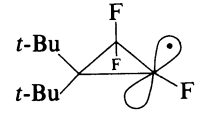


(6)

Steric effects also play a role in determining whether a cyclopropyl radical will be a rapidly inverting σ radical or a π radical. Ingold and coworkers[40] have concluded from an analysis of the ESR spectra of **7** and **8** that although the radical **3** is a σ radical having a pyramidal structure, **7** is a planar π radical. Moreover, **8** is also a planar or nearly planar π radical whereas **6** is an inverting bent σ radical. The unusual configuration of **7** and **8** is believed to be due to steric repulsion between the *t*-butyl groups and the α-hydrogen or α-fluorine which is minimized in the π radicals.



(7)



(8)

Can an α-fluorine substituent reduce the inversion frequency k_i of the cyclopropyl σ radical sufficiently so that it can maintain its stereochemistry in a chemical reaction? The answer is yes, when an efficient radical trap is available so that $k_R \gg k_i$ (Scheme 1). The tin hydrides provide such an efficient radical scavenger[41] as well as the means to generate radical intermediates by their reaction with alkyl halides[42]. The reaction usually involves the use of a radical initiator such as azobisisobutyronitrile (AIBN) or di-*t*-butyl peroxide (DTBP). The reaction mechanism is depicted in Scheme 2.

$$Me_2C(CN)\text{–}N{=}N\text{–}C(CN)Me_2 \longrightarrow 2Me_2\dot{C}(CN) + N_2$$

$$Me_2\dot{C}(CN) + R_3Sn\text{–}H \longrightarrow R_3Sn^{\bullet} + Me_2CHCN$$

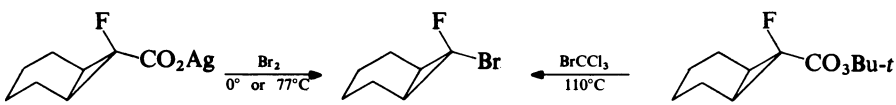
$$R_3Sn^{\bullet} + R'\text{–}X \longrightarrow R'^{\bullet} + R_3SnX$$

$$R'^{\bullet} + R_3Sn\text{–}H \longrightarrow R'\text{–}H + R_3Sn^{\bullet}$$

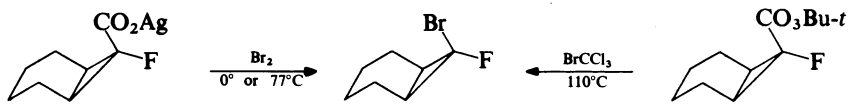
SCHEME 2

Ando and coworkers[43] reduced a series of gem-halofluorocyclopropanes with tri-*n*-butyltin hydride to yield the corresponding monofluorocyclopropanes. Table 11 lists a number of representative gem-halofluorocyclopropanes that have been reduced. The results are striking in that the reactions are completely stereospecific under the conditions specified. The effect of the α-fluoro substituent in reducing the inversion frequency (k_i) of the radical combined with the propensity of the tin hydride to react rapidly with the radical[41] best accounts for these observations.

Kaplan[44] has compared the hydrogen-transfer ability of various Group IV hydrides toward radicals and found the order (k_R) $R_3Sn\text{–}H > R_3Ge\text{–}H > R_2Si\text{–}H > R_3Si\text{–}H$. Yamanaka[45] has shown that the same order is followed in the reduction of 1-bromo-1-fluoro-2-phenylcyclopropane. Whereas using tri-*n*-butyltin hydride gives stereospecific reduction, the use of di-*n*-butylsilicon dihydride gave slightly less retention (97%) and with tri-*n*-butylsilicon hydride the retention was reduced to 84%. Ando, Yamanaka and coworkers[46] have also demonstrated that the brominative decarboxylation (Hunsdiecker reaction) of the silver α-fluorocyclopropanecarboxylate derivatives **9** and **10** proceeds in a

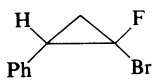
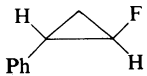
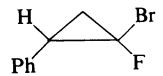
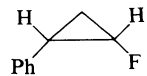
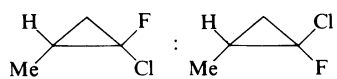
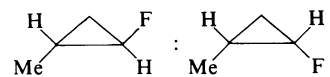
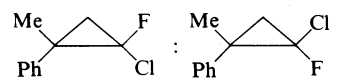
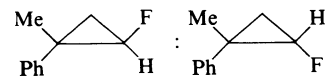
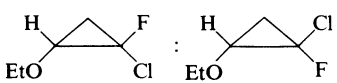
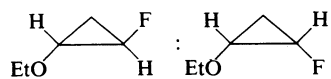
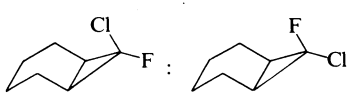
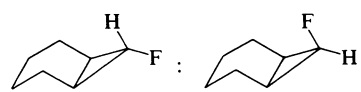
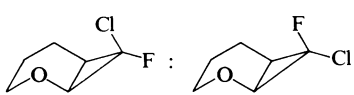
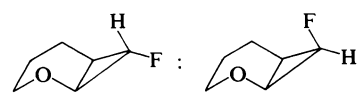


(9) (13) (11)



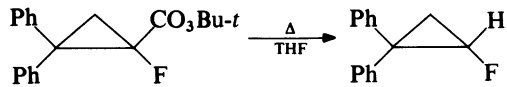
(10) (14) (12)

TABLE 11. Stereochemistry of reduction of gem-halofluorocyclopropane with tri-*n*-butyltin hydride[43]

Isomer(s) reduced	Isomer ratio	T(°C)	Product(s)	Isomer ratio
	100:0	135		100:0
	100:0	135		100:0
	66:34	90		67:33
	52:48	135		53:47
	60:40	85		61:39
	58:42	90		58:42[a]
	61:39	80		65:35

[a] Na/NH_3 reduction was also stereospecific; see M. Schlosser, G. Heinz and L. Y. Chan, *Chem. Ber.*, **104**, 192 (1971).

stereospecific manner. This again reflects the ability of an α-fluorine substituent to stabilize the configuration of a cyclopropyl radical and suggests that the bromine radical is also an efficient radical trap. Moreover, they have shown that the thermal decomposition of *exo*- and *endo*-*t*-butyl 7-fluoronorcarane-7-peroxycarboxylates **11** and **12** in $BrCCl_3$ also produced the corresponding 7-bromo-7-fluoronorcaranes **13** and **14** with 100% retention of configuration. Replacing $BrCCl_3$ as a solvent by a poorer radical trap solvent, such as toluene and cumene, reduced the stereospecificity by only 6–10%. Walborsky and Collins[47] found that the thermal decomposition of *t*-butyl (−)-(*S*)-1-fluoro-2,2-diphenylcyclopropanepercarboxylate (**15**) in tetrahydrofuran, a markedly inferior radical scavenger solvent, resulted in the formation of (−)-(*S*)-1-fluoro-2,2-diphenylcyclopropane (**16**) of overall retained configuration but only 47% optical purity, or 74% retention of configuration.

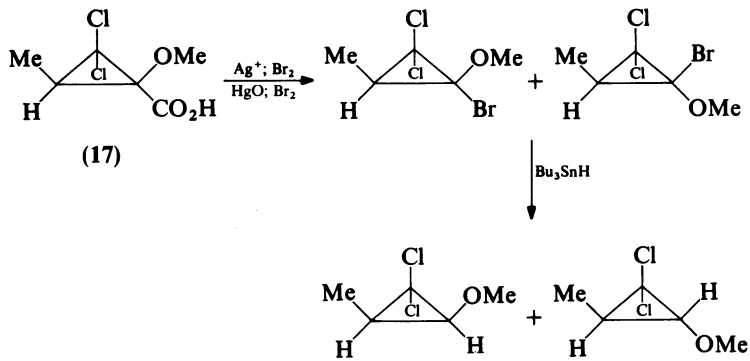


(−)-(*S*)-(**15**) (−)-(*S*)-(**16**)

In summary, the α-fluoro substituent on a cyclopropyl radical has a marked effect on the ability of the radical to maintain its configuration. A strongly electronegative atom decreases the inversion frequency k_i of the cyclopropyl σ radical and in the presence of a good radical scavenger makes $k_R \gg k_i$ (Scheme 1) and results in a high retention of configuration.

c. Methoxyl

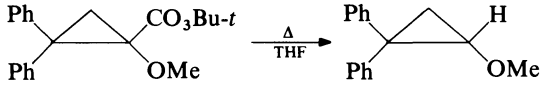
An α-methoxyl group would also be expected to stabilize the configuration of the cyclopropyl radical since oxygen is an electronegative atom. There have been two investigations of the methoxyl group as a substituent. Ando and coworkers[48] reported on the Hunsdiecker reaction of *r*-1-methoxy-*c*-2-methyl-*c*-3,*t*-3-dichlorocyclopropanecarboxylic acid (**17**). At 0°C use of either the silver salt or the Cristol–Firth method (HgO) and bromine yielded a ~ 57:43 mixture of the bromo isomers with overall retention of configuration. However, at 77°C a ~ 39:61 ratio of isomers was produced indicating overall inversion of configuration. Unfortunately, decomposition of the *r*-1-methoxy-*t*-2-methyl-*c*-3,*t*-3-dichlorocyclopropanecarboxylic acid was not studied to ascertain whether the product ratios represented a thermodynamically or kinetically controlled reaction. That the reaction is probably thermodynamically controlled was indicated by tri-*n*-



(**17**)

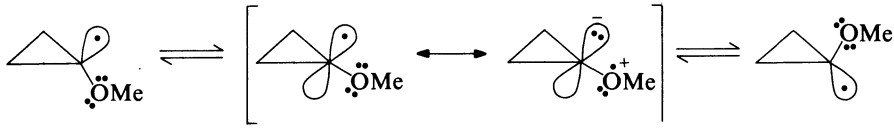
butyltin hydride reduction of each of the isomers resulting from the Hunsdiecker reaction. Both isomers at 0°C gave approximately the same ratio (54:46) of products.

Walborsky and Collins[47] decomposed chiral *t*-butyl (−)-(*S*)-1-methoxy-2,2-diphenylcyclopropanepercarboxylate (**18**) in tetrahydrofuran and isolated, *inter alia*, (−)-(*S*)-1-methoxy-2,2-diphenylcyclopropane (**19**) with an optical purity of 8% or an overall retention of configuration of 54%.



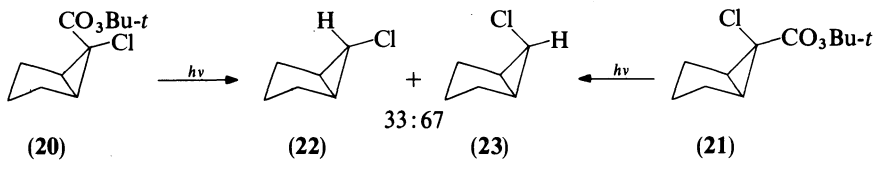
(−)-(*S*)-(**18**) (−)-(*S*)-(**19**)

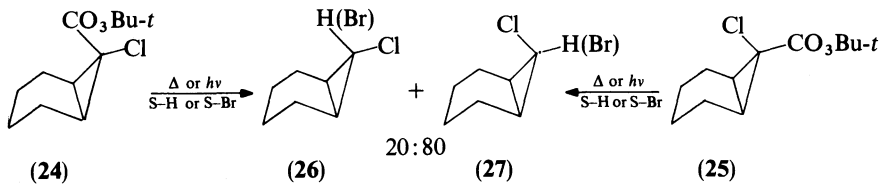
The results of these limited experiments suggest that an α-methoxyl group is not very effective in stabilizing the configuration of the cyclopropyl radical[49] and indicate that delocalization of the radical by the methoxyl group may be making a significant contribution to the stabilization of the π-radical intermediate or transition state.



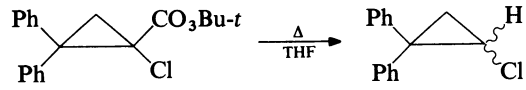
d. Chlorine, bromine and iodine

Singer and Chen[50] demonstrated the inability of an α-chlorine substituent to stabilize the configuration of a cyclopropyl radical. They showed that the photochemical decomposition of both *exo*- (**20**) and *endo*-*t*-butyl 6-chlorobicyclo[3.1.0]hexane-6-percarboxylate (**21**) in diisopropylbenzene resulted in an identical mixture of *exo*- (**22**) and *endo*-6-chlorobicyclo[3.1.0]hexane (**23**). A similar result[46] was obtained in the thermal decomposition of both *exo*- (**24**) and *endo*-*t*-butyl 7-chlorobicyclo[4.1.0]heptane-7-percarboxylate (**25**). In solvents such as toluene, cumene or bromotrichloromethane the same ratio (20:80) of *exo*-**26** and *endo*-**27** products was formed within experimental error.



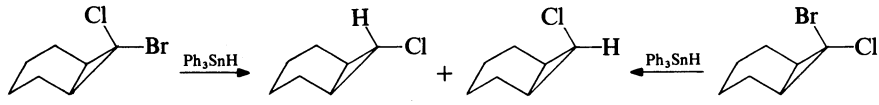


These observations are supported by the findings that the thermal decomposition of *t*-butyl (+)-(*S*)-1-chloro-2,2-diphenylcyclopropanepercarboxylate (**28**) in tetrahydrofuran resulted in completely racemic 1-chloro-2,2-diphenylcyclopropane (**29**)[47].



(+)-(*S*)-(**28**) (+)-(**29**)

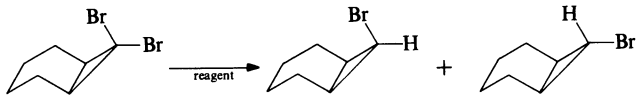
Surprisingly, the Hunsdiecker reaction using the silver salts of *exo*- and *endo*-7-chlorobicyclo[4.1.0]heptanecarboxylic acids and bromine at 0°C did not result in the same ratio of products but instead showed a high retention to inversion ratio of 88:12 for the *exo* acid and 88:12 for the *endo* acid[46]. This anomalous result may be a reflection of the bromine radical's ability to trap the cyclopropyl radical but this is unlikely. Altman and Baldwin[37] as well as Ando and coworkers[51] found that the reduction of each of the isomers of 7-bromo-7-chlorobicyclo[4.1.0]heptane, **30** and **31**, respectively, by the excellent radical scavenger triphenyltin hydride resulted in an identical mixture (21:79) of *exo*-(**32**) and *endo*-7-chlorobicyclo[4.1.0]heptane (**33**). This ratio of products is, within experimental error, identical with that found in the thermal decomposition of *exo*- and *endo*-*t*-butyl 7-chlorobicyclo[4.1.0]heptane-7-percarboxylate[46] in cumene.



(**30**) (**32**) (**33**) (**31**)

The reduction of 7,7-dibromobicyclo[4.1.0]heptane (**34**) by a variety of radical reactions leads to a similar product ratio of *exo*- (**36**) and *endo*-7-bromobicyclo[4.1.0]heptane (**35**) (Table 12). The product ratio is similar to that found for *exo*- and *endo*-7-chloro-7-bromobicyclo[4.1.0]heptane[37].

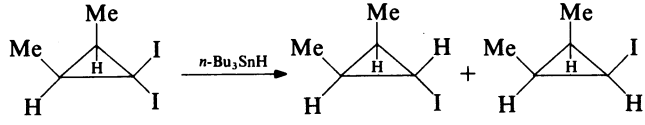
TABLE 12. Stereochemistry of the reduction of 7,7-dibromobicyclo[4.1.0]heptane



(**34**) (**35**) (**36**)

Reagent	*Endo*(%)	*Exo*(%)	Ref.
n-Bu_3SnH	72	28	52
$LiAlH_4$	75	25	53
$NaBH_4$	64	36	54
MeMgBr	72	28	55a
NaH/HMPT	67	33	55b

The only example of iodine as an α-substituent is that reported by Oliver and Rau[56]. The reduction of 1,1-diiodo-*cis*-2,3-dimethylcyclopropane (**37**) by tri-*n*-butyltin hydride yielded a 72:28 ratio of *cis* and *trans* products, a result comparable to that found for an α-chloro or an α-bromo substituent.

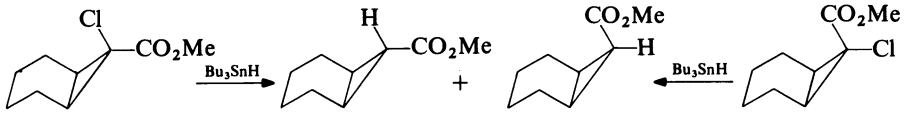


(37) 28:72

The available evidence points to the conclusion that α-chloro, α-bromo and α-iodo substituents on a cyclopropyl radical do not help to maintain its configuration. The radical is either a rapidly inverting σ-radical or a π-radical due to delocalization of the radical through the use of available d orbitals of the halogens (Cl, Br, I).

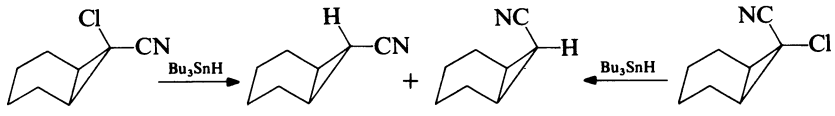
e. Carbomethoxyl and cyano

As expected, delocalizing substituents such as carbomethoxyl and cyano should decrease the barrier to inversion and perhaps may even convert the rapidly inverting σ radical to a linear π radical. The net result should be a loss of configuration. Ando and coworkers[51] have shown this to be the case in the tri-*n*-butyltin hydride reduction of the isomeric *exo*- (**38**) and *endo*-7-chloro-7-carbomethoxybicyclo[4.1.0]heptane (**39**). Both isomers gave the same (7:93) ratio of *exo*- (**40**) and *endo*-methyl bicyclo[4.1.0]heptane-7-carboxylate (**41**).



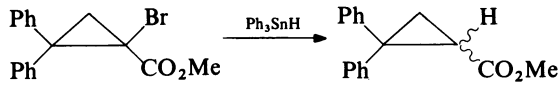
(39) (40) (41) (38)

A similar result was obtained in the reduction of each of the isomeric *exo*- (**42**) and *endo*-7-chloro-7-cyanobicyclo [4.1.0] heptane (**43**). Both isomers gave the same (6:94) ratio of *exo*- (**44**) and *endo*-7-cyanobicyclo[4.1.0]heptane (**45**).



(43) (44) (45) (42)

The triphenyltin hydride reduction of methyl (−)-(*R*)-1-bromo-2,2-diphenylcyclopropanecarboxylate (**46**) resulted in essentially racemic methyl 2,2-diphenylcyclopropanecarboxylate (**47**)[57].

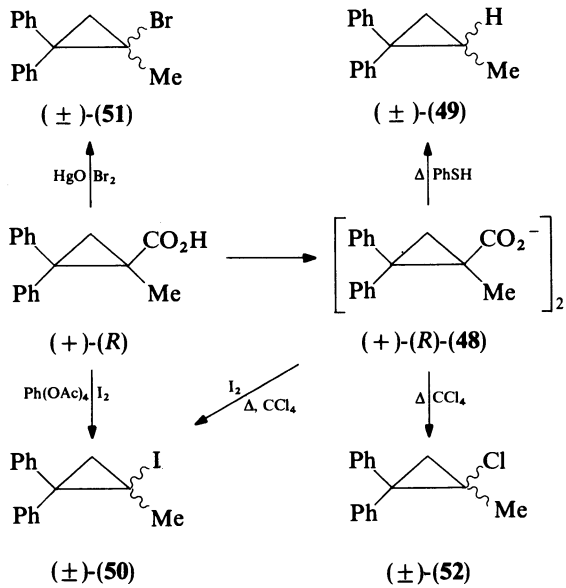


(−)-(*R*)-(**46**) (±)-(**47**)

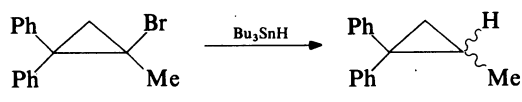
f. Methyl and trifluoromethyl

The accumulated evidence indicates that an α-methyl substituent attached to the cyclopropyl radical has very little, if any, effect in helping to maintain the configuration of

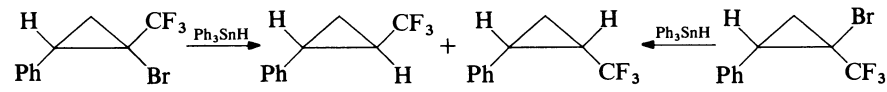
the radical. It has been shown[58,59] that thermal decomposition of the diacyl peroxide of (+)-(*R*)-1-methyl-2,2-diphenylcyclopropanecarboxylic acid, (+)-(*R*)-(**48**) in THF yielded, *inter alia*, the hydrocarbon 1-methyl-2,2-diphenylcyclopropane (**49**) which was essentially racemic. Moreover, thermolysis in carbon tetrachloride produced racemic 1-chloro-1-methyl-2,2-diphenylcyclopropane (**52**) and even the addition of a good radical trap such as iodine produced only racemic 1-iodo-1-methyl-2,2-diphenylcyclopropane (**50**). The latter reaction presumably involves the formation of an intermediate hypoiodite which decomposes to the iodide by a radical pathway. Other reactions, which presumably involve similar intermediates, are the lead tetraacetate–iodine procedure for the decarboxylation of carboxylic acids[60] and the Cristol–Firth[61] reaction (HgO/Br_2 in CCl_4). Both reactions yield the corresponding racemic iodide (**50**) and bromide (**51**)[58,59] from (+)-(*R*)-1-methyl-2,2-diphenylcyclopropanecarboxylic acid.



Further attempts to trap the chiral 1-methyl-2,2-diphenylcyclopropyl radical, before inversion, by using excellent radical scavengers as solvents were also abortive. Decomposition of the diacyl peroxide (**48**) in thiophenol and reduction of (−)-(*R*)-1-bromo-1-methyl-2,2-diphenylcyclopropane (**51**) with tri-*n*-butyltin hydride as solvent resulted in essentially racemic hydrocarbon (**49**)[58,59].



As was discussed earlier, although the CF_3 group is an electronegative substituent its influence on stabilizing the configuration of a cyclopropyl radical is similar to that of a methyl group rather than a fluorine atom[38]. Thus, Altman and Vederas[62] have shown that the reduction of *r*-1-bromo-1-trifluoromethyl-*c*-2-phenylcyclopropane (**53**) and of its

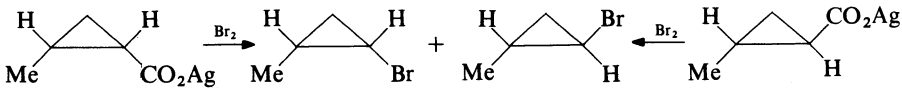


(53) (55) (54)

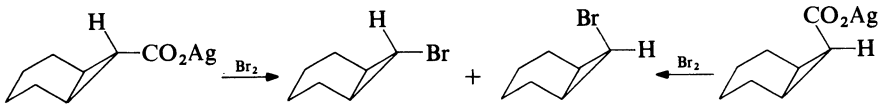
isomer **54** with a large excess of neat triphenyltin hydride gives rise to complete configurational equilibration of the radical: in both reactions the isomers of **55** have been found in a 70:30 *trans/cis* ratio.

g. Hydrogen and deuterium

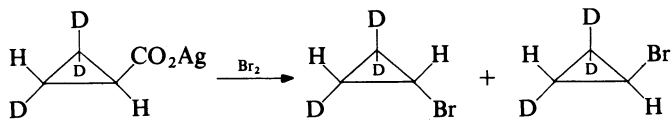
Hunsdiecker reaction of the silver salts of both *cis*-(**56**) and *trans*-2-methylcyclopropanecarboxylic acid (**57**) yielded the same mixture of *cis*- (**58**) and *trans*-1-bromo-2-methylcyclopropane (**59**), thus demonstrating that the 2-methylcyclopropyl radical was incapable of maintaining its configuration[63a]. Brominative decarboxylation of the silver salts of *exo*- (**60**) and *endo*-norcarane-7-carboxylic acid (**61**) produced the same mixture (16:84) of *exo*- (**62**) and *endo*-7-bromonorcarane (**63**)[46]. Similarly, *cis*- and *trans*-silver 1,2-cyclopropanedicarboxylate gave rise to the same isomer ratio (24:76) of *cis*- and *trans*-1,2-dibromocyclopropane[64]. Consistent with these results is the report that the Hunsdiecker reaction with the silver salt of *trans*-2,2,3-d_3-cyclopropanecarboxylic acid (**64**) gives an equimolar mixture of *cis*- (**65**) and *trans*-2,2,3-d_3-cyclopropane (**66**)[63b].



(56) (58) (59) (57)

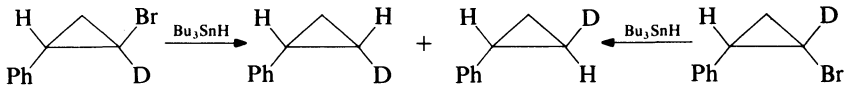


(60) (62) (63) (61)



(64) (65) (66)

Moreover, an α-deutero substituent does not have any effect on the stereochemical outcome. Both mixtures (70:30 and 3:97) of *cis*- (**67**) and *trans*-1-bromo-1-deutero-2-phenylcyclopropane (**68**) gave, upon reduction with tri-*n*-butyltin hydride, the same mixture (95:5) of *cis*- (**69**) and *trans*-1-deutero-2-phenylcyclopropane (**70**)[65].



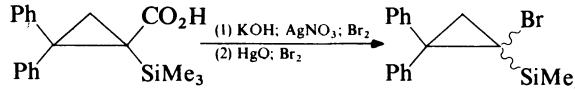
95:5

(68) (69) (70) (67)

In summary, it can be stated that both secondary cyclopropyl radicals (α-H, α-D) and the tertiary radical (α-Me) are rapidly inverting radicals incapable of maintaining their configuration.

h. Trimethylsilyl

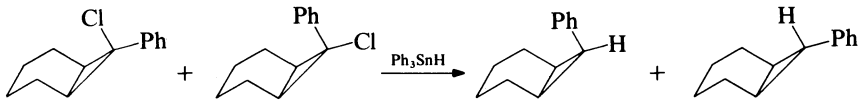
Recently, Paquette and coworkers[66a] reported on the stereochemical consequences of having a trimethylsilyl substituent at the radical site. The Hunsdiecker reaction, as well as the Cristol–Firth[56] modification thereof, on (−)-(*R*)-1-trimethylsilyl-2,2-diphenylcyclopropanecarboxylic acid (**71**) resulted in racemic (±)-1-bromo-1-trimethylsilyl-2,2-diphenylcyclopropane (**72**). The trimethylsilyl group, bulky as it is, could not slow down the inversion frequency of the cyclopropyl σ radical sufficiently to prevent complete racemization. More to the point, recent[66b] ESR studies have demonstrated that the radical intermediate is planar, or nearly so.



(−)-(*R*)-(**71**) (±)-(**72**)

i. Phenyl and vinyl

Jensen and Patterson[67] have shown that a mixture of *exo*- (**74**) and *endo*-7-chloro-7-phenylbicyclo[4.1.0]heptane(**73**) was reduced with triphenyltin hydride to yield a mixture (99:1) of *endo*- (**75**) and *exo*-7-phenylbicyclo[4.1.0]heptane (**76**).

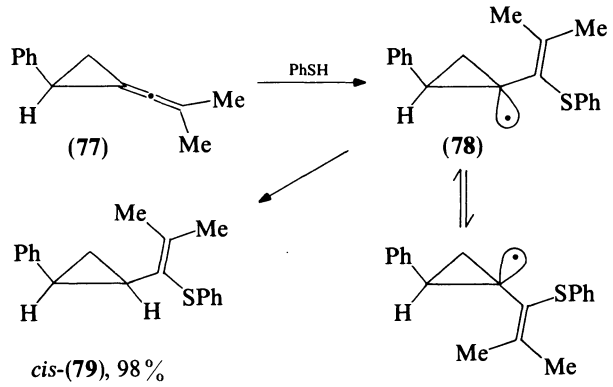


99:1

(73) (74) (75) (76)

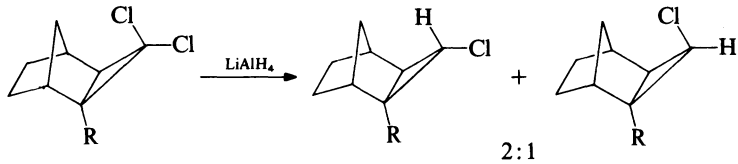
Pasto and Miles[68] have demonstrated that the regioselectivity of the radical addition of thiophenol to alkenylidenecyclopropane (**77**) is such that one generates a cyclopropyl radical having an α-vinyl substituent (**78**).

Whether these radicals are rapidly inverting σ radicals or π delocalized radicals cannot be ascertained but the almost exclusive product in both these cases is the thermodynamically less stable isomer **75** and **79**. It is in the hydrogen abstraction step that the overall stereochemistry is controlled and not by the α-substituent (see below).



2. *Effect of β-substituents*

Do β-substituents effect the stereochemistry of the cyclopropyl radical? In order to evaluate the β-substituent effect let us examine a cyclopropyl radical that can maintain its configuration, such as one with an α-fluoro as a substituent, and determine whether a β-substituent will alter its configurational stability. Inspecting the data in Table 11 one would have to conclude that β-substituents such as methyl, phenyl and ether groups have no effect on the stereochemistry of the cyclopropyl radical[67]. Also, chlorine as a β-substituent does not have any effect on the stereochemistry. Jefford and coworkers[53] have shown that $LiAlH_4$ reduction of the tricyclic compound **80** (R=H, Cl) gave the same ratio (2:1) of *anti*-



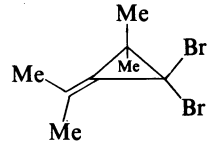
(**80**), R = H, Cl (**81**) (**82**)

81 to *syn*-**82** products. Schleyer and coworkers[69] have also concluded from their *ab initio* and MNDO calculations that β-chloro and fluoro substituents are only marginally more stable *trans* to the radical side than *cis*.

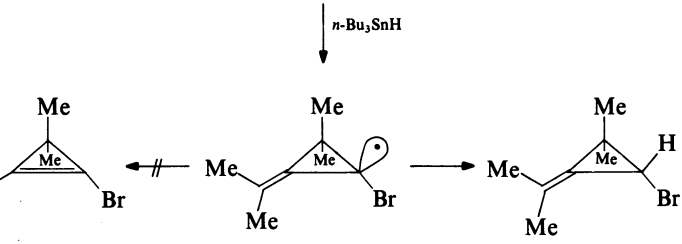
Of interest is the observation that the reduction of 1,1-dibromo-2,2-dimethyl-3-isopropylidenecyclopropane (**83**) by tri-*n*-butyltin hydride leads only to the formation of 1-bromo-2,2-dimethyl-3-isopropylidenecyclopropane (**84**) and no 1-bromo-2,2-dimethyl-3-isopropylcyclopropane (**85**)[70,71] is formed. Could it be that a π-system β to the radical site does not delocalize the π-radical intermediate of the rapidly inverting σ radical?

There are no examples of the effect of a β-vinyl group on the stereochemistry of a radical intermediate. However, a β-phenyl[65] group has been shown not to have an observable effect as far as stereochemistry or cyclization are concerned (see Table 11). An example of a β-allyl substituent is found in the tri-*n*-butyltin hydride reduction of 11,11-dibromotricyclo[4.4.1.0]undeca-3,7-diene (**86**) to a monobromo derivative (**87**). Again, there is no apparent interaction with the π-system as is evident by the lack of ring-closure product[72].

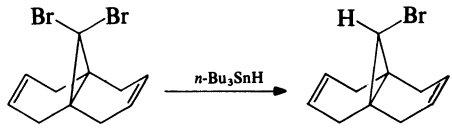
It is only when one gets to the β-homoallyl system (**88**) of Julia and coworkers[73] that one observes interaction of the cyclopropyl radical with the π-system resulting in a cyclization.



(83)

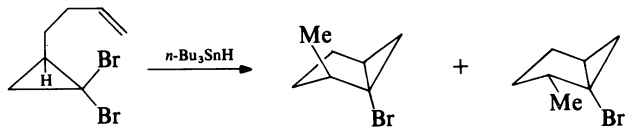


(85) (84)



(86) (87)

It should be noted that the radical cyclization proceeds to yield a five-membered ring and not a six-membered one. This is predicted by the 'Baldwin rules' for ring-closure and is classified as a 5-*exo*-trig closure[74]. $LiAlH_4$ has also been used to generate the cyclopropyl radical which also underwent a 5-*exo*-trig ring-closure[65].

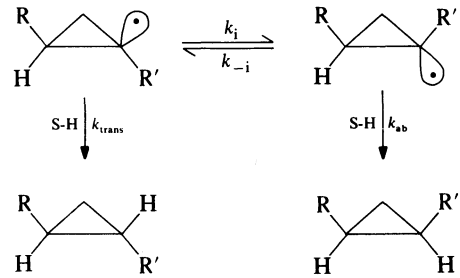


(88) *endo*, 71% *exo*, 14%

3. Regioselectivity of the rapidly inverting σ-radical

In those cases where the inversion rate (k_i) of the σ radical is faster than the trapping of the radical (k_{cis} or k_{trans}) the product(s) of the reaction will reflect the thermodynamic stability of the radical assuming that $k_{trans} = k_{cis}$ (Scheme 3).

This latter assumption is not necessary when the reaction is analyzed by ESR spectroscopy since one is observing the radical directly. Table 13 lists the structures of the thermodynamically (ESR) or chemically more favored cyclopropyl radicals. There are a number of factors which will influence the position of the equilibrium. Among them are steric effects and electronic effects. As can be seen in Table 13, entries 5, 6 and 13–21 are examples in which the position of the equilibrium is influenced by steric interactions. Entry 5 shows that the σ orbital containing the odd electron prefers to be *cis* to the phenyl group



SCHEME 3

TABLE 13. Structure of favored σ radical

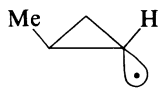
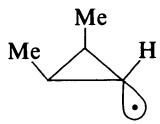
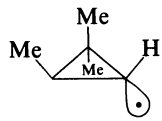
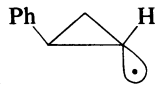
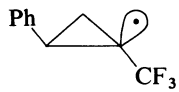
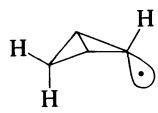
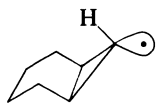
Entry	Structure	% Favored	Method[d]	Ref.
1		65	C(1)	63
2		92	C(3), C(4)	39, 75
3		80	C(2)	52
4		79	C(3)	75
5		70	C(2)	62
6[a]		mainly	C(4)	39
7		80	C(1)	46

TABLE 13. *Continued.*

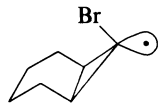
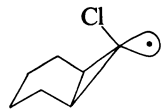
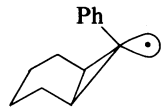
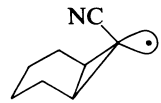
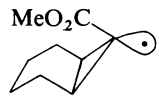
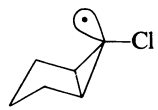
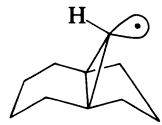
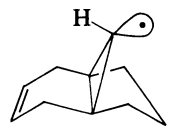
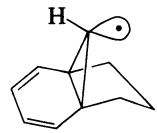
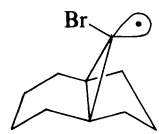
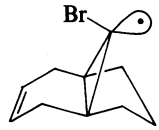
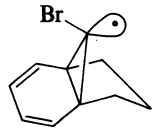
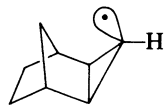
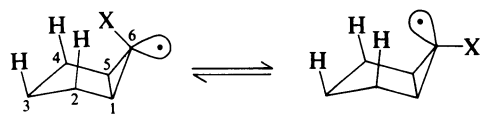
Entry	Structure	% Favored	Method[d]	Ref.
8[b]		75–80	C(1), C(5)	43
9[b]		80	C(2), C(5)	37,46
10[b]		80	C(2)	67
11[b]		92	C(2)	51
12[b]		94	C(2)	51
13[b,c]		67	C(5)	50
14		94,100	C(2)	76
15		94,100	C(2)	76
16		95	C(2)	76
17		80	C(2)	76

TABLE 13. *Continued.*

Entry	Structure	% Favored	Method[d]	Ref.
18		77	C(2)	76
19		87	C(2)	76
20		70	C(3), C(4)	39, 77
21		100	C(2)	78

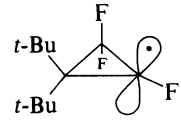
[a] Rapidly rearranges to the cyclobutenyl radical.
[b] This radical may well be a π radical.
[c] Result in toluene; opposite stereochemistry in diisopropylbenzene.
[d] C(1) (Hunsdiecker reaction); C(2) (tin hydride reduction); C(3) (dissolving metal reduction); C(4) (ESR); C(5) (acyl peroxide decomposition).

to avoid the more sterically hindered situation which would place the CF_3 and phenyl group *cis* to each other. A similar situation obtains in entries 20 and 21. Entry 13 illustrates the result of steric interaction between an *endo* substituent on C(6) and the *endo* hydrogens on C(2), C(3) and C(4). This *endo–endo* interaction is relieved when the C(6) σ-radical orbital occupies the *endo* position. This same type of interaction would account for the



results observed with the radicals shown in entries 13–19. Steric interactions not only play an important role in determining the regioselectivity of the radical but, when severe, can even cause a σ radical to be converted to a π radical. This was demonstrated by Ingold and coworkers[40] in the case of the 1,2,2-trifluoro-3,3-di-*t*-butylcyclopropyl radical (**8**) as discussed above.

One could interpret the results of entries 1–4 and 7–12 as being due to electronic effects. Dewar and Bingham[34b] have suggested that there is a stabilizing interaction between the orbital containing the odd electron and *cis* hydrogen substituents on adjacent β-carbon



(8)

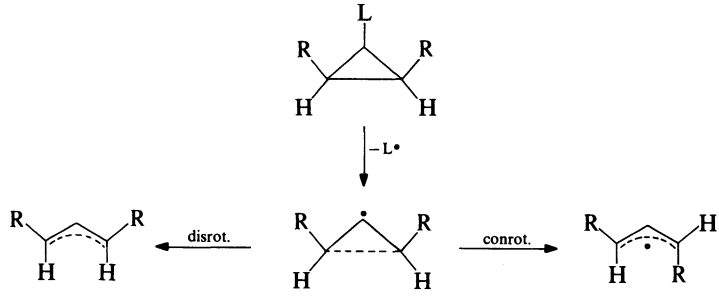
atoms. This suggestion has some support by ESR observations that there is a larger hyperfine splitting constant (hfsc) with the *cis* hydrogens than with the *trans* ones[39]. Such a stabilizing effect could account for the results observed.

The steric and electronic arguments are not all that clear cut. Without ESR evidence to the contrary one might interpret the results in entries 1–4 and 7–12 as being due to the radical being either a π radical (8–13) or rapidly inverting σ radical and that the regioselectivity observed is due to a difference in k_{cis} and k_{trans} caused by the approach of S–H from the least hindered side of the radical. At the current state of knowledge this interpretation is a possible one for these radicals but can certainly be excluded for entires 13, 20, 21 and possibly 15–19.

4. Rearrangements

The electrocyclic cyclopropyl radical–allyl radical rearrangement has been the subject of many theoretical investigations not all of which are in agreement.

Woodward and Hoffmann[79] on the basis of extended Hückel calculations suggested that the conrotatory mode is slightly preferred. At the same time Longuet-Higgins and Abrahamson[80] pointed out that both ring-opening modes were unfavorable because they are symmmetry forbidden. *Ab initio* calculations by Farnell and Richards[81] supported this latter view. Other calculations[82] led to energies of activation in the range of 30–40 kcal mol^{-1} for disrotatory opening and 40–50 kcal mol^{-1} for conrotatory opening of the cyclopropyl radical (Scheme 4).

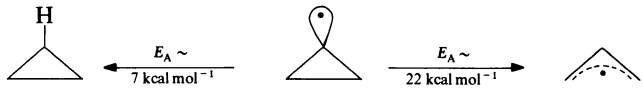


SCHEME 4

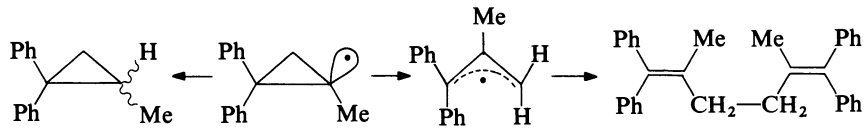
Haselbach's[83] analysis is of interest. His calculations indicated that the rupture of the ring precedes rotation of the resultant CH_2 groups. He is also in agreement with Longuet–Higgins and Abrahamson[80] that both electrocyclic modes of ring-opening are unfavorable. He favors a disrotatory opening if 'abstraction of the leaving group and ring opening occur in a concerted manner'. This qualification would exclude a concerted electrocyclic reaction since it is known from ESR observation and chemical evidence that the cyclopropyl radical exists in solution. To emphasize this point, it should be noted that in solution the unsubstituted cyclopropyl radical itself has never been observed to

rearrange to the more stable allyl radical in spite of the 30 kcal mol^{-1} stabilization predicted for this rearrangement. It is only with suitable substitution that the activation energy is lowered sufficiently to permit ring-opening.

As we have previously discussed the cyclopropyl radical is a very reactive radical. When in addition we consider the appreciable activation energy (~ 22 kcal mol^{-1})[82,84,85] necessary for the cyclopropyl radical to rearrange to the allyl radical we are not surprised that rearrangements are not always observed. The cyclopropyl radical prefers to react with solvent by abstracting hydrogen, the activation energy for which is reported[84] to be only ~ 7 kcal mol^{-1}.



Only unrearranged cyclopropyl products were reported for photochemical chlorination[27,86] and vapor phase nitration[28] of cyclopropane. The Hunsdiecker reaction of silver cyclopropanecarboxylate[87] and the thermal decomposition of cyclopropanoyl peroxide[22] also gave exclusively unrearranged product as did the di-*t*-butyl peroxide initiated decarbonylation of 1-methyl and 1-phenylcyclopropanecarboxaldehyde[26]. In general one can predict that when a good radical scavenger, solvent or substrate, is present in the reaction, unrearranged product will result (i.e. see Tables 11 and 13).

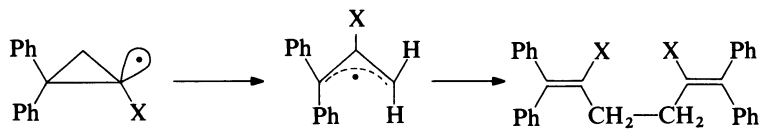


(49) **(89)**

The first example of the rearrangement of a cyclopropyl radical to an allyl radical in solution was observed in the thermal decomposition of 1-methyl-2,2-diphenylcyclopropanecarbonyl peroxide[58,59]. The radical reacted by abstracting hydrogen from solvent or by rearranging to the 1,1-diphenyl-2-methylpropenyl radical which dimerized to yield 1,1,6,6-tetraphenyl-2,5-dimethyl-1,5-hexadiene (**89**). The proportion of dimeric product to that of cyclopropane is dependent on the solvent. If a good radical scavenger is used, such as chloroform, carbon tetrachloride or thiophenol, then only the unrearranged cyclopropane derivative is obtained. This is also the case when a radical trap such as iodine is added to a benzene solution.

The ratio of dimeric product to cyclopropane product is a measure of the reactivity of the solvent toward the cyclopropyl radical. Table 14 shows the results of such a study.

Similar rearrangements have been observed with 2,2-diphenylcyclopropyl radicals that have a variety of 1-substituents[47] (Scheme 5).



X = H, Me, F, Cl, Br, OMe **(89, X = Me)**

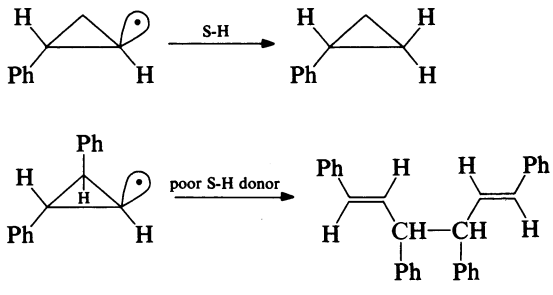
SCHEME 5

TABLE 14. Relative reactivity of various solvents toward the 1-methyl-2,2-diphenylcyclopropyl radical[59]

Solvent	Cyclopropane (%)	Dimer (%)	Relative reactivity[a] per active hydrogen
Benzene	5.85	11.95	0.23
Cyclohexane	3.98	7.14	0.30
t-Butanol	2.70	2.71	0.33
Acetone	6.77	6.77	0.51
Diethyl ether	7.37	9.61	0.57
Ethyl acetate	4.24	7.50	0.92
Toluene	7.41	8.34	1.00
Methanol	1.49	1.27	1.24
Tetrahydrofuran	6.98	6.45	1.44
Acetonitrile	8.35	4.62	1.76
Ethylbenzene	4.32	3.82	1.77
Cumene	1.45	1.77	2.50
Ethanol	3.00	1.53	3.05
2-Propanol	4.08	2.71	4.40

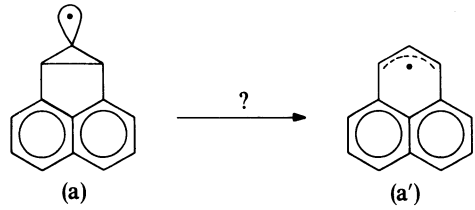
[a] Expressed in terms of reactivity of toluene as 1.

Chen[88] has demonstrated that one phenyl group in the 2-position of the cyclopropyl radical is insufficient to overcome the activation energy necessary to obtain the rearrangement. Thus thermal decomposition of *trans*-2-phenylcyclopropanecarbonyl peroxide in a poor hydrogen-donating solvent such as benzene yielded only 2-phenylcyclopropane. However, when two phenyl groups were located in the 2,3-position of the cyclopropane ring-rearranged products were obtained.

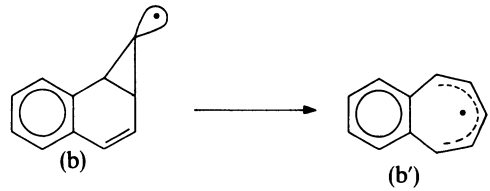


meso and *d,l*

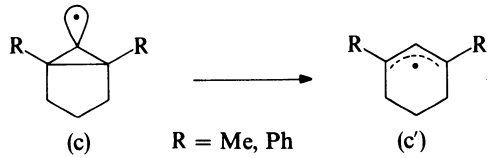
Thus, under the same conditions, thermolysis of *cis,trans*-2,3-diphenylcyclopropanecarbonyl peroxide gave a 30% yield of 1,3,4,6-tetraphenyl-1,5-hexadiene. Boche, Rüchardt and coworkers[89a] have confirmed this result. It was also shown that both *cis,cis* and *trans,trans* isomeric peroxides produced the same 1:1 mixture of *d, l*-and *meso*-rearranged products. An attempt to interpret these results on the basis of an electrocyclic ring-opening did not result in any definitive conclusion[89b]. The following cyclopropyl radicals have also been shown to undergo rearrangement. In each case the rearranged radical is a highly delocalized species thereby reducing the activation energy sufficiently for the rearrangement process to occur.



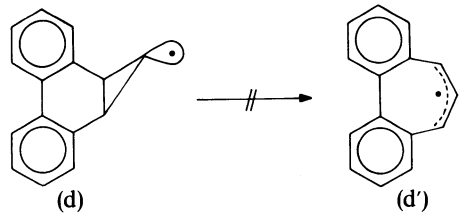
Ref. 90a, b



Ref. 91



Ref. 90b

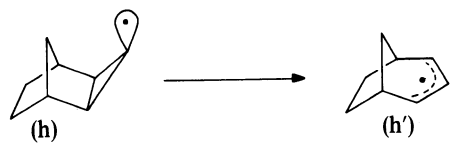


Ref. 90b

Ref. 92

Refs 93, 94

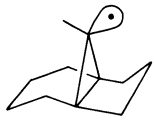
Refs 93, 94

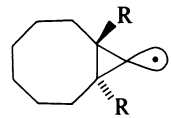


Refs 39, 77

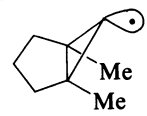
Surprisingly the dibenzonorcaradien-7-yl radical (d) is reported[90b] not to rearrange to the dibenzotropyl radical (d'), and whether the perinaphthenyl radical (a') is formed[90a, b] is also questionable[90b]. The ring-opening of 2-bicyclo[1.1.0]butyl radical (e) is not surprising[92], due to the strain and the cyclopropylcarbinyl nature of the radical. Although (f), (g) and (h) have been reported to give the rearrangement products (f'), (g') and (h')[93,94] alternative routes to the rearrangements for at least (f) and (g) have been presented[93]. Moreover, the rearranged radical (h')[39, 77] could not be detected by ESR[39] nor when generated by other means[77].

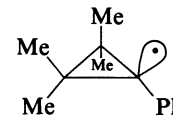
Also noteworthy is that the following cyclopropyl radicals have been reported not to undergo rearrangement (see also Table 13).





R = H, Me



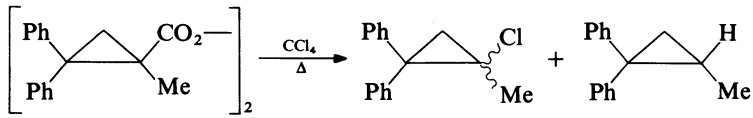


Refs: 54 95 95 95

5. *Solvent cage reactions*

With the possible exception of certain dissolving metal reactions (see Section III.B.2), the 1-methyl-2,2-diphenylcyclopropyl σ radical is incapable of maintaining its configuration in solution. In order to trap this cyclopropyl radical before complete racemization occurs, it must react at a rate equal to or greater than the inversion frequency estimated to be $\sim 10^8\ s^{-1}$. Since the average time required for diffusion from a cage has been estimated[96] to be 10^{-11} s, the most likely place to intercept a rapidly inverting σ radical would be within a solvent cage.

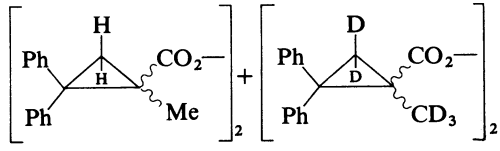
The thermal decomposition of (−)-(*R*)-methyl-2,2-diphenylcyclopropanoyl peroxide, (+)-(*R*)-**48**, in *pure* carbon tetrachloride yielded, besides the expected (±)-1-chloro-1-methyl-2,2-diphenylcyclopropane (**52**), a 2% yield of (+)-(*S*)-1-methyl-2,2-



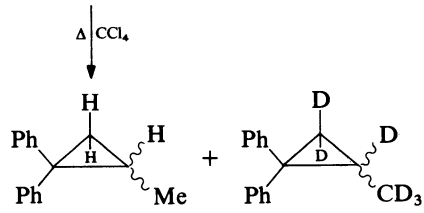
(+)-(*R*)-(**48**) (±)-(**52**) (+)-(*S*)-(**49**)

diphenylcyclopropane (**49**)[59]. Doubling the concentration of the peroxide had no effect on the yield of the hydrocarbon. Neither did addition of a good radical trap such as iodine. These observations are consistent with a solvent cage disproportionation reaction providing the hydrogen source for the formation of (+)-(*S*)-(**49**).

Finally the most definitive evidence for a cage reaction was the observation that when an equimolar mixture of the peroxide (**48**) and the peroxide-d_{10} (**48**-D_{10}) were decomposed, no crossover products were obtained; only equal amounts of fully protonated hydrocarbon (**49**) and the hydrocarbon-d_6[59] (**49**-D_6) were formed. The optical purity of the isolated (+)-(*S*)-1-methyl-2,2-diphenylcyclopropane (**49**) was found to be 31–37% with a net retention of configuration. Thus, when the lifetime of the rapidly inverting σ radical is sufficiently great to permit diffusion out of the solvent cage the product formed by the

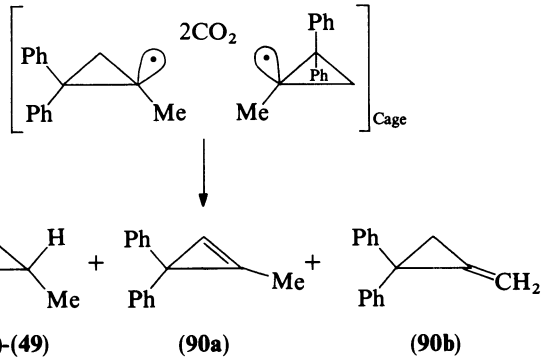


(48) (48-D_{10})



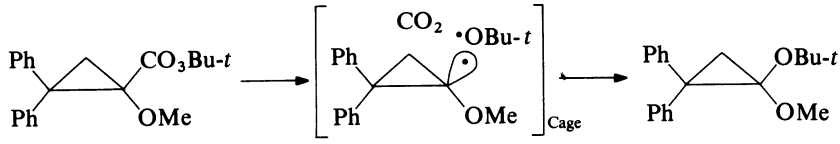
(49) (49-D_6)

radical reacting with the substrate (CCl_4) will be essentially reacemic. If the radical is constrained in a solvent cage and reacts within that cage, it will maintain its configuration to a large extent.



(+)-(*S*)-(**49**) (**90a**) (**90b**)

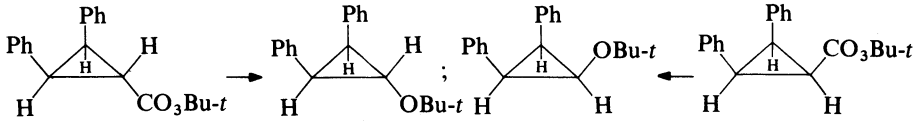
The disproportionation reaction is depicted above although other modes are possible[59]. β-Hydrogens are abstracted by the radical, either from the methyl group or the ring, to yield the hydrocarbon **49** with largely retained configuration and also the two olefins **90a, b**. A cage disproportionation reaction has also been observed in the thermal decomposition of *trans*-2-phenylcyclopropanoyl peroxide in carbon tetrachloride.



(−)-(*S*)-(**18**) (−)-(*R*)-(**91**)

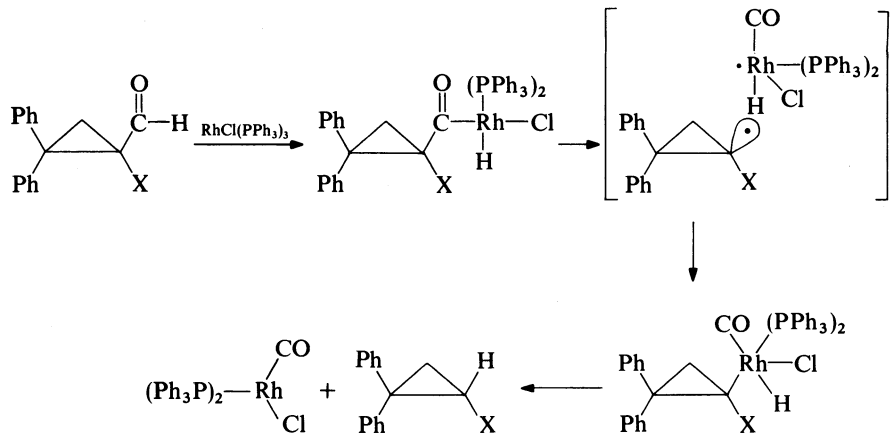
Similarly, a cage recombination reaction takes place in the thermal decomposition of *t*-butyl (−)-(*S*)-methoxy-2,2-diphenylcyclopropanepercarboxylate (**18**)[47]. A 0.8% yield of 1-*t*-butoxy-1-methoxy-2,2-diphenylcyclopropane (**91**). $[\alpha]_{Hg}^{24} = 63°C$, was isolated from

the reaction mixture. Unfortunately, neither the absolute configuration nor the optical purity of the cage product was determined. The magnitude of the rotation would indicate that a high degree of retention of optical activity had occurred. In line with previous cage reactions the configuration is probably maintained as well.



(92) (93) (95) (94)

Thermal decomposition of *t*-butyl *trans,trans*-2,3-diphenylcyclopropanepercarboxylate (**92**) in ethylbenzene yielded (10%) exclusively *trans,trans*-2,3-diphenylcyclopropyl *t*-butyl ether (**93**) as a cage recombination product, whereas the *cis,cis* isomer (**94**) gave a low yield of recombination product consisting of 1% *trans,trans* **93** and 1.5% *cis,cis* **95**. The low yield and the loss of stereoselectivity in the latter case are thought to be due to a steric effect[89].



SCHEME 6

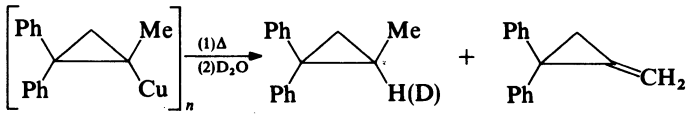
It has been proposed that the decarbonylation of aldehydes by the Wilkinson catalyst [$RhCl(PPh_3)_3$] involves a radical pair disproportionation or recombination reaction[97]. A radical pair intermediate in solution is equivalent to a cage reaction (Scheme 6). Table 15 shows the results obtained from the decarbonylation of a series of chiral cyclopropyl aldehydes[92,98].

TABLE 15. Decarbonylation of chiral 1-X-2,2-diphenylcyclopropanecarboxaldehyde[97]

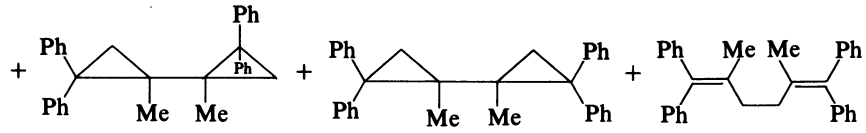
X	Config.	Product. config.	% Optical purity
Me	(−)-(*R*)	(−)-(*S*)	94
Cl	(−)-(*S*)	(−)-(*S*)	83
F	(−)-(*S*)	(−)-(*S*)	73
OMe	(−)-(*S*)	(−)-(*S*)	6

6. *Aggregates (clusters)*

The thermal reaction of chiral (*S*)-1-(methyl-2,2-diphenylcyclopropyl)copper (**96**) provides an interesting example of the effect of aggregates on the stereochemistry of the cyclopropyl radical[99]. The thermal decomposition of (*S*)-**96** led to the formation of a variety of products depicted in Scheme 7. Product analysis, including stereochemistry, led to the mechanism shown in Scheme 8. The aggregate mixture $[(S)\text{-}\mathbf{96}]_n$ is assumed to exist in THF solution (colloidal?) where $n = 2$, 4, or 6.



(*S*)-(**96**) (−)-(*R*)-(**49**) 28% (**90b**) 1%

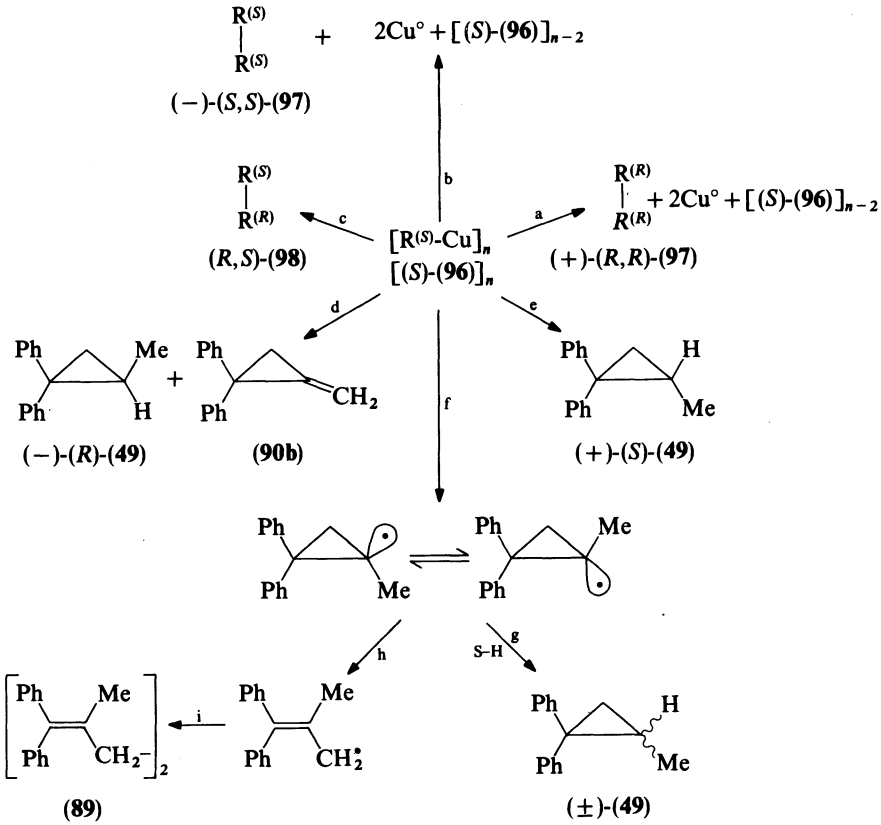


(+)-(*R*,*R*)-(**97**) 27%, and 4% (−)-(*S*,*S*)-(**97**) (*R*, *S*)-(**98**) 19% (**89**) 5%

SCHEME 7

The aggregates have been shown to be stable at 0°C for at least 1 h and are viewed as molecular species which exist in a solvent cage of THF. Upon thermolysis a homolytic cleavage of two $R^{(S)}$–Cu bonds occur (R = 1-methyl-2,2-diphenylcyclopropyl and superscript (*S*) or (*R*) relates to configuration) with the formation of Cu° and the concomitant coupling within the solvent cage (reaction a), of $R^{(S)}$ to yield (+)-($R^{(R)}$, $R^{(R)}$)-**97** with retention of configuration. If within the cage one of the $R^{(S)}$ rotates 180°, this would lead to the formation of $R^{(R)}$, and coupling $R^{(S)}$ and $R^{(R)}$ would produce *meso*-(*R*, *S*)-**98** (reaction c). If two $R^{(S)}$ rotate 180° and then couple, this would lead to the formation of (−)-(*S*, *S*)-**97** (reaction b); combination with (+)-(*R*, *R*)-**97** results in the production of *racemic compound* (±)-(*R*, *R*/*S*, *S*)-**97**.

By itself, the formation of **97** takes on great significance. Its formation has never been observed in solution, only the products resulting from the reactions a, b and i, are observed[58, 59]. Also the 1-methyl-2,2-diphenylcyclopropyl radical does not dimerize to **97** even in a cage reaction[59] but instead it follows the usual course of a tertiary σ radical, it disproportionates. The only other time that dimerization of this radical has been observed was when the radical was formed on a magnesium metal surface[100]. *Thus, the reaction of the aggregates* $[(S)\text{-}(\mathbf{96})]_n$ *resembles a surface reaction* (see below).



SCHEME 8. Thermal decomposition of (*S*)-(1-methyl-2,2-diphenylcyclopropyl) copper (**96**) (R = 1-methyl-2,2-diphenylcyclopropyl)

III. ANION RADICALS

A. Introduction

In this section we are dealing predominantly with reactions of cyclopropyl halides with metal surfaces (heterogeneous) and with dissolving metals in solution (homogeneous). Although cyclopropyl metal bonds result from these reactions it is information regarding the *intermediates* leading to the formation of these metal bonds that we are seeking. Are radicals and/or radical anions formed as intermediates? What are the differences between heterogeneous and homogeneous reactions?

B. Electron Transfer to σ Bonds of Cyclopropyl Halides

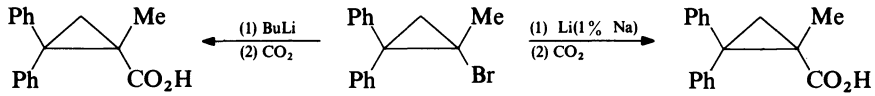
1. Surface reactions

a. Lithium surface

The stereochemical results of radicals generated in solution and at metal surfaces can vary greatly. For example, genesis of the 1-methyl-2,2-diphenylcyclopropyl σ radical in

solution, by decomposing its chiral diacyl peroxide precursor, leads to formation of completely racemic product. This is so even when good radical traps such as iodine or thiophenol are present[58, 59] (*vide supra*). By contrast reaction of chiral (+)-(*S*)-1-bromo-1-methyl-2,2-diphenylcyclopropane (**51**) with lithium metal followed by carbonation leads to the formation of (−)-(*S*)-1-methyl-2,2-diphenylcyclopropanecarboxylic acid (**99**) with 73% retention of configuration[100] (45% optical purity).

It was shown that the loss of configuration was not due to racemization of the lithium reagent, once formed in solution, since the preparation of the same lithium reagent by halogen–lithium exchange of the bromide **51** with butyllithium produced, after carbonation, the acid **99** with 100% retention of configuration. Halogen–lithium exchange was shown to proceed with complete retention of configuration and the 1-methyl-2,2-diphenylcyclopropyllithium produced in this manner was shown to be configurationally stable at ambient temperatures and over extended periods of time[101].



(−)-(*S*)-(**99**) 100%

(+)-(*S*)-(**51**)

(−)-(*S*)-(**99**) 73%

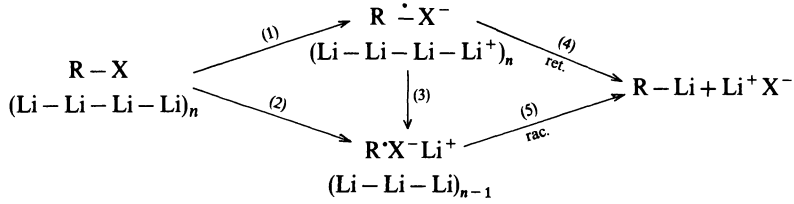
The nature of the lithium surface is important. Varying the particle size of the lithium dispersion from 25 μm with a surface area of 2782 cm^2 to 150 μm with a surface area of 464 cm^2 reduced the optical purity of the resulting acid by nearly 50%. It was also demonstrated that the amount of sodium impurity in the lithium dispersion had a significant effect not only on the stereochemical results of the metallation reaction but also on the reactivity of the metal surface itself. For example, reaction of chiral 1-iodo-2,2-diphenylcyclopropane with 25 μm lithium dispersions containing 0.002%, 0.02% and 1% sodium yielded after carbonation 1-methyl-2-cyclopropanecarboxylic acid (**99**) with optical purities of 13%, 16% and 36%, respectively. The increase in optical purity with increase in sodium content may be a consequence of lowering the ionization potential of the metallic surface[102].

The stereochemistry of the reaction is also dependent on the halogen. The reaction of chiral 1-halo-2,2-diphenylcyclopropane with 25 μm lithium dispersions containing 1% sodium produced the results shown in Table 16. It should be noted that the optical purity of the acid varies in the same order as the carbon–halogen bond strength Cl > Br > I.

TABLE 16. Lithiation of chiral 1-halo-1-methyl-2,2-diphenylcyclopropane followed by carbonation to give **99**

Substrate	Halide	Temp. (°C)	Time (min)	Acid yield (%)	Optical purity
52	Cl	25	40	73	63
51	Br	26	42	70	45
50	I	25	41	60	36

The following mechanism[100] was proposed by Walborsky and Aronoff in 1965 for the lithiation reaction (Scheme 9). The stereochemistry of the reaction may be explained by a single electron transfer (SET) to the carbon–halogen bond which results in either the formation of an ion paired halide radical anion on the metal surface (pathway 1) or what is

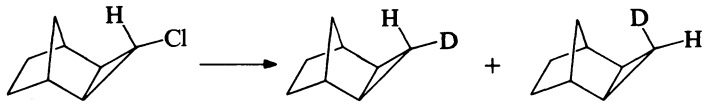


SCHEME 9. A mechanistic scheme for the formation of lithium reagent

in essence a Li^+X^- complexed loose radical pair (pathway 2). The radical anion can collapse (pathway 4) to form lithium reagent with retention of configuration or dissociate (pathway 3) to the complexed loose radical pair. The radical (R·) in the complexed loose radical pair can undergo rotation before the next SET occurs and this would yield the racemic lithium reagent. As the halogen (X) is changed from iodide to bromide to chloride reaction pathways 1 and 4 are favored and result in a decrease in the amount of complexed loose radical pair formation. Moreover, increasing the surface area and/or decreasing the ionization potential (increased sodium content) would also favor pathways 1 and 4 resulting in an increase of retention of configuration.

In solution the 1-methyl-2,2-diphenylcyclopropyl σ radical racemizes[58, 59] but when the radical is formed at the surface via intermediate ion radical precursors and/or complexes, the overall result is a retention of configuration. It may therefore be dangerous to draw conclusions about the stereochemical fate of σ radicals under these conditions[103]. For example, *cis*- and *trans*-1-bromo-2-methylcyclopropane when treated with metallic lithium yield products with 8–38% retained configuration[104]. In one interpretation[104] it was claimed that the observed retention of configuration is due to the intrinsic stability of the intermediate σ cyclopropyl radical. More likely, the retention is due to a surface effect[102] as described above since it has previously been shown that the Hunsdiecker reaction with both *cis*- and *trans*-2-methylcyclopropanecarboxylic acids gave identical mixtures of products[63] thus demonstrating that the 2-methylcyclopropyl radical is incapable of maintaining its configuration in solution (at least under the Hunsdiecker conditions).

The effect of surface has also been demonstrated in the reduction[77] of *anti*-3-chloro-*exo*-tricyclo[3.2.1.$0^{2,4}$]octane (**100**). When the reduction is carried out by lithiation in ether followed by deuterolysis the ratio of *syn* product **102** to *anti* product **101** was about 2:1 whereas reduction under homogeneous conditions, lithium naphthalenide followed by deuterolysis, resulted in a 30:1 ratio. Again, there is greater retention on the metal surface. The *syn* σ radical was shown to be the thermodynamically more stable (Table 13).



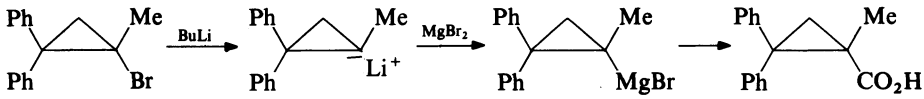
anti-(**100**) *anti*-(**101**) *syn*-(**102**)

b. Magnesium surface

In 1961 it was reported that the reaction of chiral 1-bromo-1-methyl-2,2-diphenylcyclopropane (**51**) with magnesium metal produced a partially optically active Grignard reagent[105]. It was suggested that the racemization observed occurred in the Grignard formation step. In 1964 it was also established[106] that the racemization occurred

at some stage preceding Grignard formation by showing that once the Grignard reagent was formed it was optically stable. This was accomplished by preparing the Grignard reagent from the optically stable lithium reagent[101] by treatment with anhydrous magnesium bromide followed by carbonation. The acid produced in this manner was optically pure.

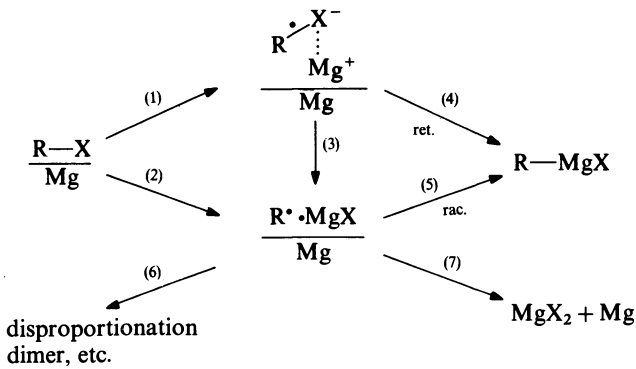
There is no doubt that the 1-methyl-2,2-diphenylcyclopropyl σ radical is incapable of maintaining its configuration when it is formed in solution[58, 59]. How then can one



(+)-(*S*)-(**51**) (−)-(*S*)-(**99**)

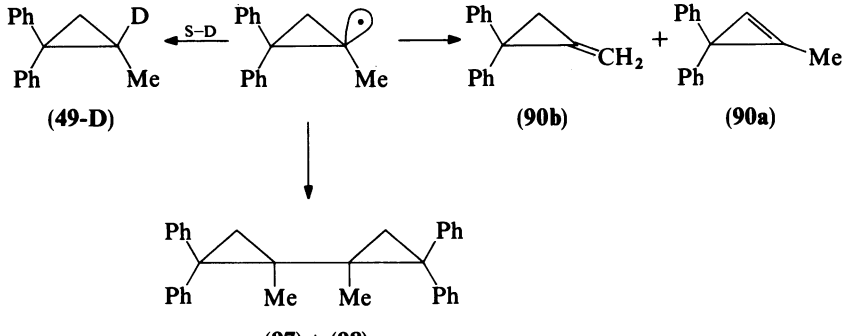
account for the retention of configuration and optical activity that is observed? In 1964 Walborsky and Young[106a] proposed the mechanism of Grignard formation (Scheme 10) which was elaborated upon in 1973[106b].

The processes pictured in Scheme 10 take place at the magnesium–metal solution interface. Interaction of the cyclopropyl halide and magnesium by pathway 1 involves electron transfer from the metal into the antibonding carbon–halogen bond to give a radical anion in close association with a univalent magnesium cation (ion paired radical anion). Collapse of this tight anion radical–cation radical pair, pathway 4, leads to Grignard reagent formation with complete rentention of configuration. Alternatively collapse may proceed by pathway 3 to a loose radical pair (M·MgX complexed loose radical pair) which may also be formed directly by pathway 2. Bodewitz and coworkers[107] have provided CIDNP evidence for pathway 2. It is in the complexed loose radical pair that racemization can take place. Combination of the cyclopropyl radical with the magnesious halide radical produces largely racemic Grignard reagent (pathway 5). The kinetic analysis of Grignard formation by Whitesides and coworkers[108] is also consistent with pathway 1 and/or 2 being involved in the rate-determining step.



SCHEME 10. A mechanistic scheme for Grignard reagent formation

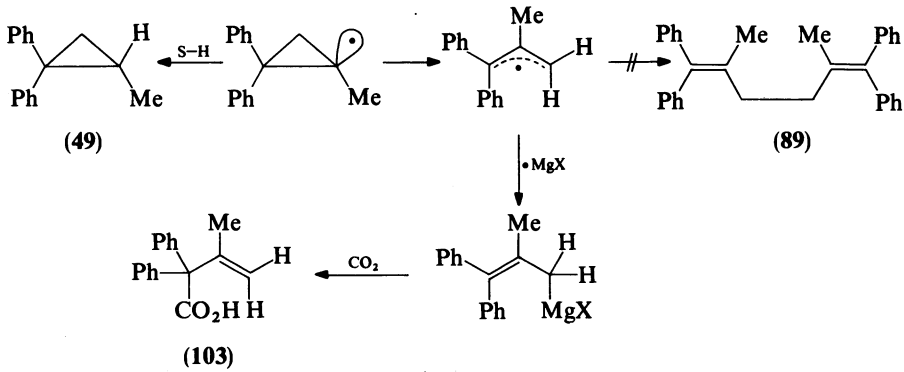
The cyclopropyl radical may, however, escape capture by the magnesious halide and undergo typical radical reactions of disproportionation (**90a**, **90b**) and dimerization (**97**, **98**) (pathway 6), all at or very close to the surface. Or, some radical may leave the surface interface and abstract a hydrogen atom from the solvent. Consistent with the



(49-D) (90b) (90a)

(97) + (98)

surface nature of the reaction is the observation that very little ring-opened product is observed. When the radical is generated in ether solution by thermal decomposition of the diacyl peroxide, the products consist of the cyclopropyl hydrocarbon and a dimeric product resulting from ring-opening[58, 59]. The only ring-opened product appears in the acid fraction, after carbonation of the Grignard solution. The allyl radical produced by the ring-opening does not dimerize as allyl radicals in solution normally do but rather is captured by the magnesious halide.



(49) (89)

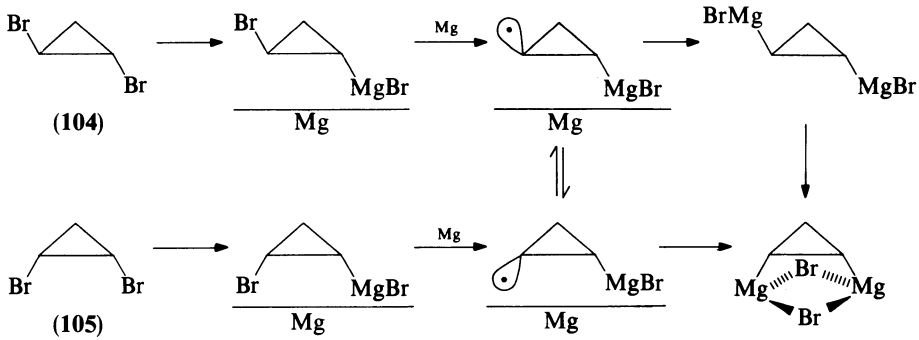
(103)

Further confirmation of the surface nature of Grignard formation is the observation that when THF-d_8 and diethyl ether-d_{10} were used as solvent only 28% and 6% deuterium, respectively, were found in the hydrocarbon fraction of the reaction[100]. The source of hydrogen atoms is the disproportionation of the surface radicals. Moreover, the yield of hydrocarbons from reaction in THF is only ~ 1.0–1.5% whereas in diethyl ether the yield is 20%. This is in accord with the greater solvating power of THF[109] which removes the metal organic species from the surface of the magnesium. Recent XPS analysis of the Grignard formation reaction is consistent with the surface nature of the reaction[110].

The effect of halogen X is evident in both the stereochemistry and the amount of Grignard reagent formed. The energy of the carbon–halogen bond increases in the order I < Br < Cl as do the optical purities (2%, 17% and 26% respectively) and yields of Grignard reagent (35%, 70% and 89% respectively). This is consistent with the amount of complexed loose radical pair formed at the surface, pathways 2 and 3 of Scheme 10, being determined by the strength of the carbon–halogen bond[100], i.e. the weaker the bond the greater the amount of loose radical pairs. As with lithiation the retention of configuration

and optical activity of the σ cyclopropyl radical is due to a surface interaction rather than to any intrinsic stability of the radical.

In our earlier discussion there did not seem to be any strong evidence for a stabilizing or unstabilizing effect of a β-substituent on the cyclopropyl radical. Recently Bickelhaupt and coworkers[111], in an extension of the early work of Wiberg and Bartley[112], have provided indirect evidence that a β-MgBr exerts a stabilizing interaction on the cyclopropyl radical. Both *trans*-**104** and *cis*-1,2-dibromocyclopropane (**105**) when treated with magnesium in ether and then hydrolyzed with D_2O or carbonated with CO_2 formed *cis*-1,2-dideuterocyclopropane and *cis*-1,2-cyclopropanedicarboxylic acid, respectively. Based on this observation it was suggested that a *cis*-β-MgBr stabilized the σ-radical intermediate, which in turn would lead to the formation of a stabilized *cis*-α,β-dibromomagnesium cyclopropane. The stabilized *cis*-β-MgBr σ radical has received support from *ab initio* calculations of Schleyer and coworkers[69] in which they determined that the *cis* isomer is 1.6 kcal mol^{-1} more stable than the *trans*. The reaction can be viewed as occurring on the surface[113] of the magnesium. After forming the first bond with the magnesium, the reagent is associated with the surface long enough to permit formation of the 1,2-dimagnesium bromide via radical pair pathway resulting in the formation of the thermodynamically more stable *cis* isomer (Scheme 11). As Bickelhaupt[111] has suggested because of the unique double bromine bridging[111, 112] and the entropic advantage of less ether fixation any *trans* isomer formed may be converted to *cis*.

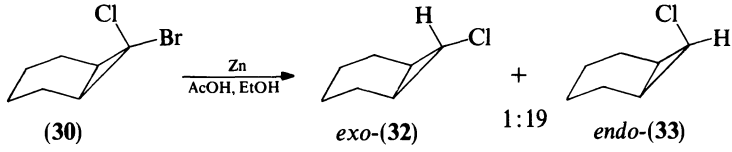


SCHEME 11. Reaction of 1,2-dibromocyclopropane with magnesium

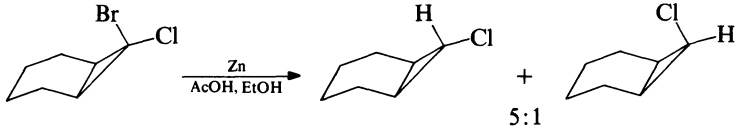
c. Zinc surface

Triphenyltin hydride reduction[37] of either isomer of *exo*-7-bromo-*endo*-7-chlorobicyclo[4.1.0]heptane (**30**) and *endo*-7-bromo-*exo*-7-chlorobicyclo[4.1.0]heptane (**31**) resulted in an identical 1:4 mixture of *exo*-**32** and *endo*-7-chlorobicyclo[4.1.0]heptane (**33**). This same ratio was also obtained when *exo*-**24** and *endo*-*t*-butyl 7-chlorobicyclo[4.1.0]heptane-7-percarboxylate (**25**) were thermally decomposed in cumene[46]. As previously discussed the α-chlorocyclopropyl σ radical, generated in solution, is incapable of maintaining its configuration and the 1:4 *exo*:*endo* product ratio represents the thermodynamically controlled reaction mixture (Table 13). By contrast, the reaction of *exo*-7-bromo-*endo*-7-chlorobicyclo[4.1.0]heptane (**30**) with zinc in an acetic acid–ethanol mixture yielded a mixture of *exo*-**32** and *endo*-7-chlorobicyclo[4.1.0]heptane (**33**) with an *exo*:*endo* ratio of 1:19. This amounts to a heavily preferred retention of configuration for the reduction and a ratio of products far from that expected for a thermodynamically controlled reaction. Moreover, the *endo*-7-bromo isomer (**31**), under the same reaction conditions, gave an *exo*-**32**:*endo*-**33** ratio of 5:1 for the product mixture

of *exo*-**32** and *endo*-7-chlorobicyclo[4.1.0]heptanes. Again, a preferred retention of configuration is observed, with the thermodynamically less stable isomer predominating[114].

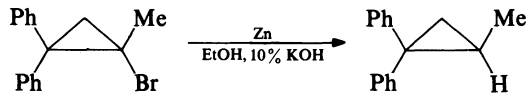


(**30**) *exo*-(**32**) *endo*-(**33**)



(**31**) *exo*-(**32**) *endo*-(**33**)

Annino and his coworkers[114] have postulated a mechanism for the reaction at the zinc surface patterned after the one proposed by Walborsky and coworkers for Grignard formation[100,106]. The organozinc intermediate formed is rapidly hydrolyzed by the protonic solvent. Note also that the reaction of zinc, in ethanol–10% KOH, with chiral 1-bromo-1-methyl-2,2-diphenylcyclopropane (**51**) yielded 1-methyl-2,2-diphenylcyclopropane (**49**) with 21% retention of configuration[115], a result comparable to the 15% retention that is found in Grignard formation.

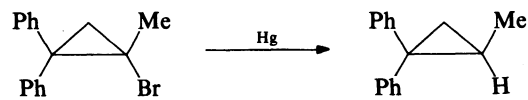


(+)-(*S*)-(**51**) (−)-(*R*)-(**49**)

d. Mercury surface

As a first approximation one can view metallation and electrolytic reduction as a single class of reactions differing only in the ease with which electrons are transferred to the substrate. Ordinarily mercury metal does not react with alkyl halides because of its high ionization potential of 240 kcal mol^{-1} as compared with 124, 176 and 216 kcal mol^{-1} for lithium, magnesium and zinc, respectively. However, if one places a potential across mercury then it will readily react with alkyl halides in an electrolytic reaction.

Controlled potential electrolysis[116] of (+)-(*S*)-1-bromo-1-methyl-2,2-diphenylcyclopropane (**51**) in acetonitrile at −2.7 volts vs. SCE yielded the hydrocarbon



(+)-(*S*)-(**51**) (−)-(*R*)-(**49**)

(−)-(*R*)-1-methyl-2,2-diphenylcyclopropane (**49**) with an optical purity of 25%. Current integration indicated that 1.98 electrons per molecule reacted. The reduction involves two single electron transfers (SET).

The reduction is viewed as occurring in the following manner[117].

(1) $RBr + e^- \rightarrow [R\text{–}Br]^{\cdot -}$

(2) $[R\text{–}Br]^{\cdot -} \rightarrow R^{\cdot} + Br^-$

(3) $R^{\cdot} + e^- \rightarrow R^-$

(4) $R^{\cdot} + Hg^{\circ} \rightarrow RHg_n^{\cdot}$

(5) $RHg_n^{\cdot} + e^- \rightarrow R^- + Hg^{\circ}$

(6) $RHg_n^{\cdot} + RHg_n^{\cdot} \rightarrow RHg_{2n}\text{–}R \rightarrow RHgR + Hg_{2n-1}^{\circ}$

(7) $RHgR + e^- \rightarrow R^- + RHg^{\cdot} \xrightarrow{Hg^{\circ}} RHg_n^{\cdot}$

(8) $R^- + CH_3CN \rightarrow R\text{–}H + {}^-CH_2CN$

(9) $R^- + Et_4N^+Br^- \rightarrow R\text{–}H + CH_2{=}CH_2 + Et_3N + Br^-$

As in direct metalation, the reaction occurs at the metal surface. An electron is transferred from the surface to the σ^* antibonding orbital of the carbon–bromine bond to produce the anion radical in the rate-determining step[114,116] (equation 1). The anion radical can then dissociate at the surface to the 1-methyl-2,2-diphenylcyclopropyl radical (equation 2). At this point some racemization may occur and the radical can undergo a number of indistinguishable reactions. The radical may pick up another electron to yield the anion (equation 3) or since mercury is such an efficient radical trap, the radical may become adsorbed on the mercury surface (equation 4) from which it can either take another electron to yield the anion (equation 5) or combine with another adsorbed radical to produce a dicyclopropylmercury (equation 6).

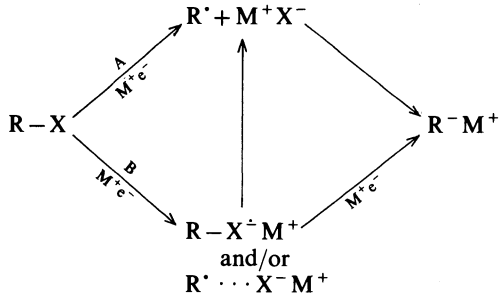
The formation of the dicyclopropylmercury alone or in combination with the adsorbed radical type intermediates accounts for the observation that the substrate disappears at a faster rate than the reduction product appears[116]. The dicyclopropylmercury can then accept an electron to produce the anion and a cyclopropylmercury radical which in combination with the mercury surface becomes an adsorbed radical (equation 7) which can be recycled through the pathway of equation 5 or equation 6. The anions formed in equation 3, equation 5, and equation 7 react at the surface with acetonitrile solvent (equation 8) to yield the hydrocarbon. When deuterated acetonitrile was used the hydrocarbon isolated contained 76% deuterium[116]. The anion can also react with the electrolyte, tetraethylammonium bromide, in an elimination reaction (equation 9) to produce hydrocarbon, ethylene and triethylamine, all of which have been identified in the reaction mixture[116].

The surface reaction of lithium metal with the same chiral (−)-(*S*)-bromide (**51**) produces a product which has retained its optical activity to the extent of 46%[100]. Reaction with magnesium results in 15–18% retention of optical activity with overall retention of configuration[105]. The observation that the hydrocarbon produced in electrolytic reduction has retained 25% of its optical activity (63% retention of configuration) is consistent with the proposed surface nature of this reaction.

The controlled potential electrolysis of *endo*-7-bromo-*exo*-7-chlorobicyclo[4.1.0]heptane (**31**) and *exo*-7-bromo-*endo*-7-chlorobicycyclo[4.1.0]heptane (**30**) resulted in a mixture of *exo*-**32** and *endo*-7-chlorobicyclo[4.1.0]heptane (**33**) in which the retention–inversion ratio was 2.6:1 in each case. Overall retention of configuration is the usual observation[114]. However, this need not always be the case, since by changing the substituent at the reductive center from methyl in bromo-1-methyl-2,2-diphenylcyclopropane (**51**) to a carboxyl or carbomethoxyl group, the resulting product was still optically active (30–40%) but the configuration was inverted[115].

2. *Dissolving metal reductions (homogeneous)*

The reduction of alkyl halides by solutions of dissolved metals like, e.g. sodium in ammonia or alkali metal naphthalenides in tetrahydrofuran, provides a convenient means of removing halogens to produce hydrocarbons or to prepare alkali metal organic compounds. It is generally accepted that these reductions involve free radical intermediates $R^{\bullet}$, (pathway A, Scheme 12)[118].



X = halide; M = alkali metal

SCHEME 12. Dissolving metal reductions

Are ion paired halide radical anions $R–X^{\bullet-}M^{+}$ and/or weak radical · · · XM complexes $R^{\bullet}\cdots X^{-}M^{+}$ also intermediates in such ET reactions (pathway B, Scheme 12)?

This timely question[119] is dealt with mainly in Section III.B.2.b.

a. Reductions in liquid ammonia

It is well established that lithium and sodium derivatives of 1-methyl-2,2-diphenylcyclopropane are capable of retaining their optical activity and configuration[100,101]. It has also been shown that when the corresponding radical is generated in solution the resulting product is racemic[58,59]. Only in a solvent cage[59] and on metal surfaces[100,102,105,106] can this rapidly inverting σ cyclopropyl radical be intercepted.

Because of these observations a study of optically active 1-halo-1-methyl-2,2-diphenylcyclopropanes with solutions of sodium in liquid ammonia was undertaken[120]. As will be seen, the stereochemical results observed were shown to be dependent on the concentration of sodium in ammonia, the nature of the halogen and a heterogeneity factor.

The chemical composition and physical properties of solutions of sodium in liquid ammonia have been known to depend upon the concentration. In particular, physical measurements have generally shown that such solutions pass from blue solutions where they contain essentially free solvated electrons at very high dilution (0.003 M), through dilute solutions having salt-like characteristics (0.003–1.0 M), to bronze solutions that behave as metals at very high concentrations[121]. The reduction of (+)-(*S*)-1-bromo-1-methyl-2,2-diphenylcyclopropane (**51**) using a highly diluted solution (0.026 M) of sodium in liquid ammonia yielded, *inter alia*, essentially racemic hydrocarbon (**49**). On the other hand, when a concentrated solution (6.5 M) was used the hydrocarbon produced was 46% optically pure with overall retention of configuration. These results are consistent with the interpretation that under highly diluted conditions the cyclopropyl radical is produced in solution and before the second SET occurs it racemizes. At high concentrations, ('metallic

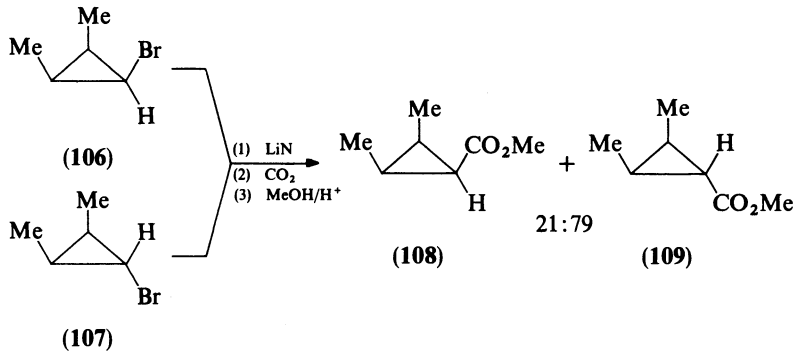
bronze') the reaction is occurring at the metallic surface leading to a stereochemical result comparable to that observed with metallic sodium in ether[100,101].

The effect of halogen on the stereochemical course of the reduction is in the same order as that observed on metallic surfaces. The optical purity of the hydrocarbon **49** using a 4 M solution of sodium in liquid ammonia, decreases in going from chloride (58%) to bromide (43%) to iodide (17%).

The above interpretation would seem adequate to account for the results. However, the reaction is of greater complexity and may involve the surface of the *crystalline halide* instead of the metal surface. If instead of adding crystalline chiral (+)-(*S*)-1-bromo-1-methyl-2,2-diphenylcyclopropane (**51**) to a 3–4 M solution of sodium in ammonia to obtain the hydrocarbon of 43% optical purity, one adds an ammoniacal solution of the bromide **51** to the dissolving metal solution then the resultant hydrocarbon **49** is completely racemic. It is tempting to speculate that the observed optical activity in the product, when crystals are used, is due to the radical being formed and trapped at the surface of the crystal lattice. It is noteworthy that the crystals turn deep red as soon as they are added to the dissolving metal solution. Since most organic halides have limited solubility in liquid ammonia these results point to a danger in the interpretation of results obtained in such media. However, it is clear that when the 1-methyl-2,2-diphenylcyclopropyl σ radical is produced in solution under highly diluted dissolving metal conditions (Na/NH_3) it is incapable of maintaining its configuration and that its inversion frequency is greater than a second SET[75].

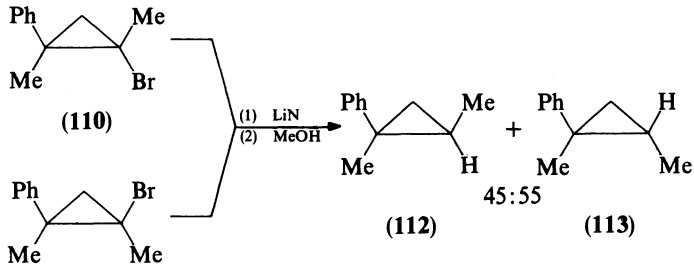
b. Reductions with alkali metal naphthalenides

Boche and coworkers[122] have reported that *r*-1-bromo-*c*-2,*c*-3-dimethyl- as well as *r*-1-bromo-*t*-2,*t*-3-dimethylcyclopropane (**106** and **107**), reacted with lithium naphthalenide (LiN) in THF and after carboxylation and methylation gave the identical 21:79 mixture of the corresponding carbomethoxy derivatives **108** and **109**. A completely analogous result was obtained with another secondary cyclopropyl bromide, *cis*- and *trans*-1-bromo-2-phenylcyclopropane[75].



The reduction of tertiary cyclopropyl halides with alkali metal naphthalenides leads to a similar situation. After treatment of a 78:22 and a 25:75 mixture, respectively, of *r*-1-bromo-1-methyl-*c*-2-methyl-*t*-2-phenylcyclopropane (**110**) and its isomer (**111**) with LiN in THF at 20°C, protonation with methanol led to identical 45:55 mixtures of *r*-1-phenyl-1,*c*-2-dimethyl- and *r*-1-phenyl-1,*t*-2-dimethylcyclopropanes (**112** and **113**).

Reactions of *r*-1-chloro-1-methyl-*t*-2-phenylcyclopropane (**114–Cl**) and *r*-1-chloro-1-methyl-*c*-2-phenylcyclopropane (**115–Cl**) as well as of **114–Br** and **115–Br** with lithium, sodium and potassium naphthalenide (MN), respectively, demonstrate that neither the



variation of the halide nor of the naphthalenide gegenion has any significant influence on the isomer ratio of the resultant *cis*- and *trans*-1-methyl-2-phenylcyclopropanes (**116** and **117**) (Table 17)[122]. Results of Freeman[77] and Ledlie and coworkers[123] fully confirm these findings.

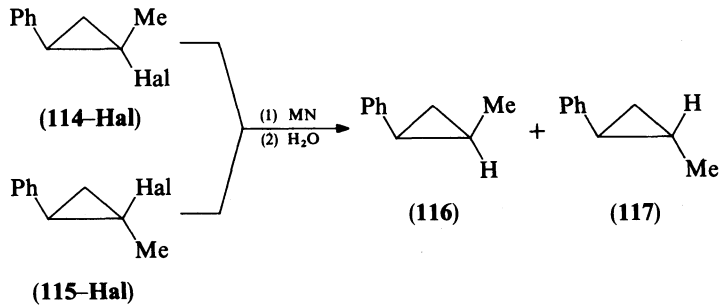


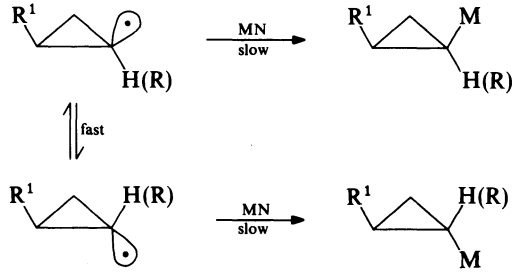
TABLE 17. Ratios **116**/**117** from the reactions of **114–Hal** and **115–Hal** with MN in THF at room temperature[122]

MN	**114–Cl**	40:60 **114–Cl/115–Cl**	**114–Br**	68:32 **114–Br/115–Br**
LiN	45:55	45:55	45:55	45:55
NaN	40:60	40:60	40:60	40:60
KN	39:61	39:61	39:61	39:61

The entirely different pathway of reduction in homogeneous solution and on a surface is nicely illustrated by a result of Dewar and Harris[104]. Reaction of **106** (**107**) with lithium metal leads to 54 (31)% of *r*-1-lithio-*c*-2,*c*-3-dimethylcyclopropane—the precursor of **108**. As shown earlier, in the homogeneous LiN reductions, both bromides give 21% of **108**.

Thus, the results in solution with the cyclopropyl halides mentioned lead to the following conclusions:

(1) Free secondary and tertiary cyclopropyl radicals reach their thermodynamic equilibrium before they are trapped by a *bimolecular* SET reaction from the alkali metal naphthalenides to give a configurationally stable alkali metal species. Net retention is not observed under such conditions (Scheme 13).



SCHEME 13. Alkali metal naphthalenide reductions of cyclopropyl halides

This is in agreement with the general observation that the equilibration of isomeric cyclopropyl radicals is always faster than any of the known bimolecular trapping reactions of these radicals in solution.

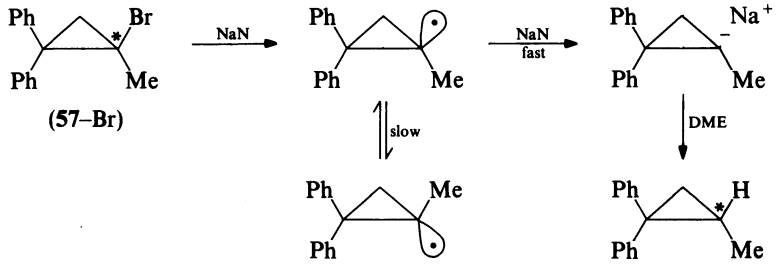
(2) Assuming a similar rate constant for the reactions of cyclopropyl radicals with MN in THF as for the reaction of primary alkyl radicals with NaN in dimethoxyethane (DME) ($k = 1.6 \cdot 10^9\ l\,mol^{-1}$)[124a] the rate constant for the inversion of secondary and tertiary cyclopropyl radicals is $k \geqslant 5 \cdot 10^9\ s^{-1}$ corresponding to $\Delta G^{\neq} \leqslant 3.7$ kcal mol^{-1}. This is in good agreement with the ESR results of Fessenden and Schuler[8] and Kawamura and coworkers[39].

(3) There is no experimental indication that either an ion paired cyclopropyl halide radical anion ($CprX^{\cdot-}\ M^+$) and/or cyclopropyl radical $\cdots$ XM complex ($Cpr^{\cdot} \cdots XM$) participate in the product-determining step of these homogeneous bimolecular SET reactions. Kinetically all that would be required is that the reactivity of these species with one halide ion should differ from that with another[125a]. This is clearly not the case as shown in Table 17. Rather, the C–X bond is broken before the product partitioning step (Scheme 13). Either the halide containing species decompose very rapidly or dissociative SET takes place to give cyclopropyl radicals directly[119,124,125]. This is not unexpected since Garst came to the same conclusions for the reactions of 'normal' alkyl halides with sodium naphthalenide[124c].

An entirely different result has been reported by Jacobus and Pensak[126]. They found that the reduction of the optically active 1-bromo-1-methyl-2,2-diphenylcyclopropane (**51**) with sodium naphthalenide (NaN) in DME (0.5 M) yields the corresponding hydrocarbon **49** of 29% optical purity with net retention of configuration. This observation was interpreted to mean that the 1-methyl-2,2-diphenylcyclopropyl σ radical was being captured by a second SET from sodium naphthalenide to give the sodium derivative (which transforms in DME to **49**) at a rate faster than its inversion frequency (Scheme 14).

In the light of the results discussed previously (*vide supra*) for the halides **106**, **107**, **110**, **111**, **114–Hal** and **115–Hal**, and many others, this interpretation seems unlikely. The following study of Boche and colleagues clearly demonstrates that the experimental results of Jacobus and Pensak are correct but that their interpretation is flawed[122].

Table 18 summarizes the net retentions of configuration of the cyclopropane **49** observed in the reactions of the optically active cyclopropyl halides **50–52** with alkali metal naphthalenides MN as the halide X, the gegenion M and the concentrations are varied. The effect of inverse versus normal addition is demonstrated in Table 19. The influence of the solvent is given in Table 20. Dicyclohexyl-18-crown-6 also affects the amount of retention of cyclopropane **49** (Table 21).



SCHEME 14. Proposed mechanism for the sodium naphthalenide reduction with retention of configuration[126]

TABLE 18. Percent net retention of configuration of cyclopropane **49** formed in the reactions of the halides **50–52** (0.9 M) with MN (0.9 M) in THF at 20 °C, followed by hydrolysis after 1 min

	LiN[a]		NaN[c]		KN[c]	
Halide	normal[a]	diluted[a]	normal[a]	diluted[a]	normal[a]	diluted[a]
52–Cl	0.2	< 0.1[100]	0.8	0.1[100]	3	1.2[100]
51–Br	32	15 [25]	49	42 [100]	53	56 [25]
50–I	57	43 [100]	48	42 [100]	41	47 [100]

[a] Normal addition (MN in THF is added dropwise to the halides in THF). Diluted solutions, e.g. [25] fold dilution: MN (0.36 M), halide (0.1 M), [ ] = dilution factor.
[b] ⩽ 1 equivalent.
[c] ⩾ 2.5 equivalents.
[d] Yields of **49**: 73 ± 16%.

TABLE 19. Percent net retention of configuration of cyclopropane **49** formed in the reactions of the halides **50–52** (0.9 M) with KN (0.9 M) in THF at 20°C, followed by hydrolysis after 1 min

	52–Cl	**51–Br**	**50–I**
Inverse[a] addition	3	53	41
Normal addition	3	53	41

[a] Inverse addition (the halide in THF is added dropwise to KN in THF).

TABLE 20. Percent net retention of configuration of cyclopropane **49** formed in the reactions of **51–Br** (0.9 M) with MN (0.9 M) in THF, DME and hexamethylphosphoric acid triamide (HMPT) (normal addition)

MN	THF	DME	HMPT
LiN	32	17	3
NaN	49	31	3
KN	53	43	2

TABLE 21. Percent net retention of configuration of cyclopropane **49** from the reactions of **51–Hal** (0.9 M) in THF with KN (0.9 M), without and in the presence of dicyclohexyl-18-crown-6 ('crown ether') (normal addition)

	Without crown ether	With crown ether
52–Cl	3	0
51–Br	53	7
50–I	41	18

The following points emerge from Tables 18–21.

(1) The amount of net retention of configuration of **49** is strongly *halogen* dependent (Table 18). In contrast to the surface reductions with, e.g. Li and Mg in which the chloride gave the highest net retention, under homogeneous conditions it is just the other way around: the chloride **52–Cl** shows almost no retention!

(2) With LiN, the iodide **50–I** gives the highest net retention but with KN it is the bromide **51–Br** that gives the highest net retention (Table 18). Thus the amount of net retention of configuration of **49** is also dependent on *the gegenion* M^+.

(3) The strong influence of *solvent* (Table 20) and *crown ether* (Table 21) on the net retention is in agreement with the dissociation of X^- *and the solvated* M^+ in the product-determining step. One would not expect such an influence with a free cyclopropyl radical in the product-determining step, as can be seen from Table 17.

(4) Normal, inverse addition (Table 18) and the dilution experiments (Tables 18 and 19) lead to almost the same amounts of net retention for **49**. This essentially excludes an involvement of a *bimolecular* SET in the product-determining step. In the case of a bimolecular reaction increasing concentrations of MN should lead to an increase of net retention in **49**.

(5) The almost negligible net retention observed in the reactions of the *chloride* **52–Cl** with LiN, NaN and KN excludes even the involvement of a cyclopropyl *radical* trapping reaction as being responsible for the distinct net retentions observed in the reductions of the bromide and the iodide **51–Br** and **50–I**, respectively.

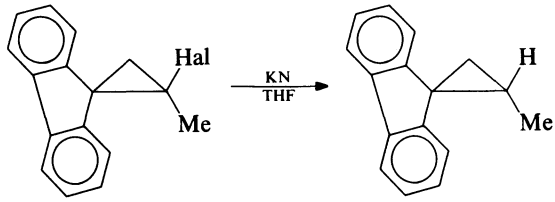
Reactions of 1-bromo- and 1-chloro-1-methyl-2,2-biphenylenecyclopropane **118–Br** and **118–Cl** with KN in THF support the findings with **50–52**: the resultant 1,1-biphenylene-2-methylcyclopropane (**119**) shows net retention of configuration, and the amount of retention is dependent on the nature of the halogen (Table 22)[122].

What is the reason for the alternative pathways in the reactions of the cyclopropyl halides **106, 107, 110, 111, 114–Hal, 115–Hal** and **50–I, 51–Br, 52–Cl, 118–Hal** with alkali metal naphthalenides?

Undoubtedly, in the case of the cyclopropyl halides **106, 107, 110, 111, 114–Hal** and **115–Hal** the normal mechanism with the cyclopropyl radical participating in the product-determining step is observed. The cyclopropyl halides **50–52** and **118–Hal**, however, seem to react in such a way that cyclopropyl halide radical anions $CprX^{\cdot-}\,M^+$ and/or cyclopropyl radical complexes $Cpr^{\cdot}\cdots X^-M^+$ are kinetically significant. The question whether species of this type indeed exist 'is an important issue'[125b].

The first experimental hint for a 'finite lifetime' of an 'alkyl halide anion radical' in homogeneous etheral solution was provided by Garst and coworkers in 1977[124b]. From the reduction of 5-hexenyl chloride, bromide and iodide with disodium tetraphenylethylene in 2-methyltetrahydrofuran (MTHF) at 20°C they concluded that radical anions $R\text{–}X^{\cdot-}\,Na^+$ were involved and that the order of their stability was $R\text{–}I^{\cdot-}Na^+ > R\text{–}Br^{\cdot-}Na^+ > R\text{–}Cl^{\cdot-}Na^+$.

TABLE 22. Percent net retention of configuration of cyclopropane **119** formed in the reactions of **118** (0.1 M) with KN (0.4 M) in THF at 20°C (normal addition)



(118–Hal) **(119)**

Hal	% Net retention
Br	75
Cl	11

Symons[125b] critically discussed the results of Garst and coworkers. He points out that although it is very unlikely that an ion paired halide radical anion $R–X^{\cdot-}M^+$ exists in the case of R = 5–hexenyl, $R^{\cdot}\cdots X^-M^+$ complexes possessing weak residual charge-transfer interactions would also be expected to differ kinetically from each other as the halide is varied. Of special significance for the interpretation of the results obtained with the *cyclopropyl* halides **50–52** and **118–Hal** are the following conclusions of Symons[125]:

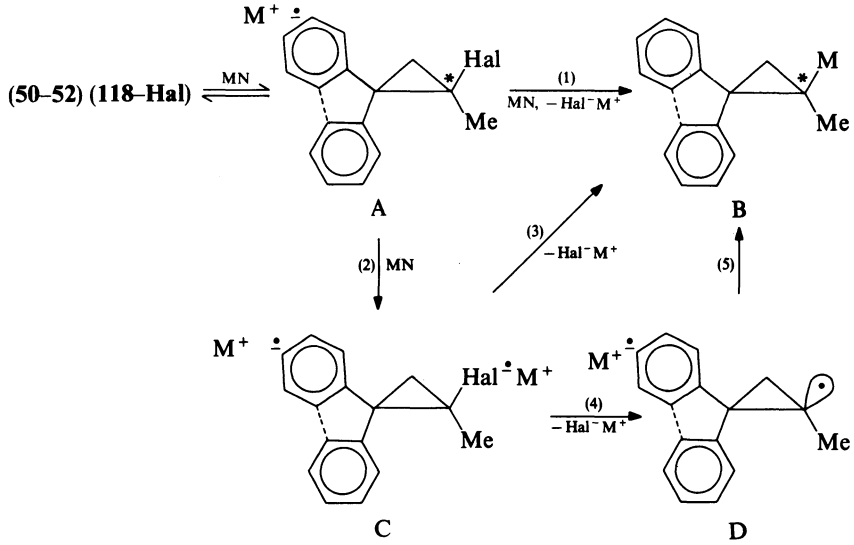
(1) Genuine σ^* radical anions exist only if the corresponding radical is naturally bent or pyramidal—as this is the case with the cyclopropyl radical but not with normal aliphatic π radicals.

(2) Since iodide I^- is the best electron donor of the halide ions, it can be expected that $R^{\cdot}\cdots I^-M^+$ will be the most thermodynamically stable of the $R^{\cdot}\cdots X^-M^+$ complexes towards dissociation[127], and the least reactive as a donor of $R^{\cdot}$. This is precisely what is observed in the homogeneous reductions that we have been discussing.

Recent model *ab initio* calculations by Clark and Illing[128a] on $MeCl^{\cdot-}M^+$ ion pairs (M = Li, Na, K) suggest a modest barrier to dissociation and not a dissociative SET. Furthermore, they clearly show the influence of different gegenions Li^+, Na^+ and K^+: the leaving group is X^-M^+ rather than X^- which is in accord with the results given in Table 18.

In agreement with the first-order kinetics in the product-determining step in the reactions of **50–52** and **118–Hal** with MN, and with all other experimental facts outlined in detail above, the following *intra*molecular SET reactions are proposed to account for the net retention observed with these cyclopropyl halides (Scheme 15).

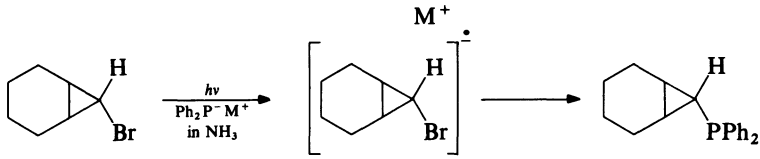
Because of the good electron accepting qualities of the two aromatic substituents in **50–52** and **118–Hal** (which are not present in the 'normal' cyclopropyl halides **106**, **107**, **110**, **111**, **114–Hal** and **115–Hal**) the first SET leads to A with the extra electron predominantly in the aromatic part of the molecule (see Section III.C), and not in the σ^* orbital of the C–X bond. The second SET may lead directly to the final product B (route 1), or to C as an intermediate (route 2). *Formation of B from C via route 3 corresponds to the intramolecular SET trapping with retention of configuration of a* $CprX^{\cdot-}M^+$ *and/or* $Cpr^{\cdot}\cdots X^-M^+$ *species and thus to a kinetic proof of their existence.* At the moment it is not clear whether a σ^* radical anion $CprX^{\cdot-}M^+$ or a cyclopropyl radical complex $Cpr^{\cdot}\cdots X^-M^+$ is trapped although a σ^* radical anion is much more likely with



SCHEME 15. Alternative pathway for the alkali metal naphthalenide reduction of the cyclopropyl halides **50–52** and **118–Hal**[122]

cyclopropyl than with 'normal' aliphatic halides[125b]. Dissociation to give D (route 4) followed by *intra*molecular trapping of the rapidly inverting cyclopropyl radical (route 5) should lead mostly to *racemic* B as indicated by the very low retentions observed with the *chlorides* **52–Cl** and **118–Cl**.

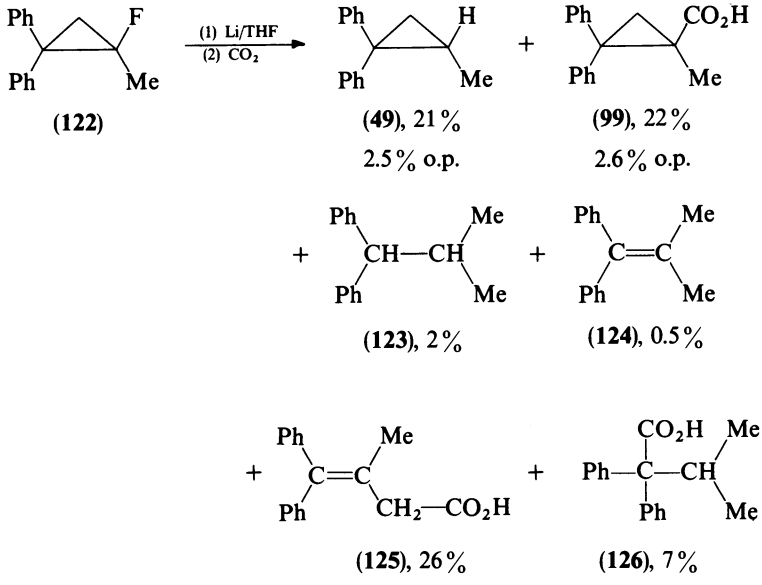
The formation of cyclopropyl halide radical anion pairs as intermediates is also invoked in $S_{RN}1$ type substitution reactions by Rossi[135] and Meijs[136]. It seems that the photostimulated reaction of cyclopropyl bromides like 7-bromonorcarane (**120**) with $Ph_2P^-M^+$ to give **121** involves a radical chain, and halogen-containing radical anions as chain carrier.



(120) (121)

In view of the results with the halides **50–52** and **118–Hal** it is not surprising that in the reaction of optically active 1-isocyano-1-methyl-2,2-diphenylcyclopropane with sodium naphthalenide in DME a similar result was observed. The cyclopropane **49** showed 13% net retention of configuration as observed by Niznik and Walborsky[137].

Walborsky and Powers also reported on the reduction of optically active 1-fluoro-1-methyl-2,2-diphenylcyclopropane (**122**) under homogeneous (sodium naphthalenide and Na/NH_3) as well as heterogeneous (lithium metal) conditions[138]. The most important outcome of this work is to show the facile acceptance of electrons by the electrophoric[139] phenyl groups causing, in this case, a substantial fragmentation of cyclopropyl C–C bonds because of the low reactivity of the C–F bond[140]. Relevant products and their distribution in the reaction with Li in THF followed by workup with CO_2 are given on the next page.



In the Na/NH_3 reduction only the ring-opened **123** was observed, while in the rather slow NaN reduction besides little cyclopropane **49** (6%) mostly the ring-opened **124** (58%) and **123** (17%) were formed. It has been pointed out before that the NaN reduction of **50–52** results only in the cyclopropane **49**. As far as the formation of the cyclopropane **49** and the acid **99** in the Li reduction of **122** is concerned, a similar mechanism has been discussed as outlined in Scheme 15 for the reduction of **50–52** and **118–Hal** in homogeneous solution. The marginal retentions of **49** (2.5% o.p.) and **99** (2.6% o.p.) are in line with the expected instability of the corresponding fluoride containing radical anion.

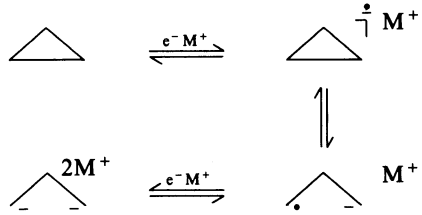
In summary, SET reactions under homogeneous conditions on the cyclopropyl halides **50–I, 51–Br, 52–Cl, 122–F**, the corresponding isonitrile and **118–Cl, Br** which are strongly halide, gegenion and solvent dependent clearly reveal a pathway with halide- and gegenion-containing intermediates (pathway B in Scheme 12). Normally—with one exception[124b]—SET reactions of this type occur exclusively via radical intermediates (pathway A, Scheme 12), as, for example, clearly demonstrated by the reactions of the cyclopropyl halides **106**, **107**, **110**, **111**, **114–Hal** and **115–Hal**.

C. Electron Transfer to π-bonded Substituents of Cyclopropanes

1. *Introduction*

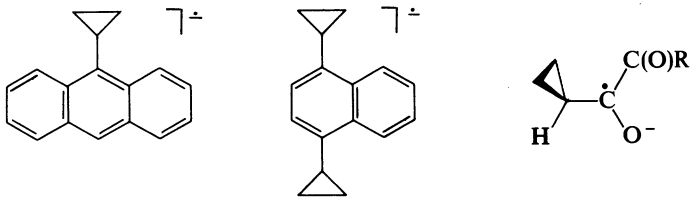
Electron transfer to cyclopropane should lead to the cyclopropane radical anion which, in principle, can isomerize to the ring-opened trimethylene radical anion. Further reduction of the trimethylene radical anion should give a 1,3-dianion. A less likely two-electron transfer to cyclopropane could conceivably give the ring-opened 1,3-dianion via the corresponding cyclopropane dianion.

The preparation of the cyclopropane radical anion was published in 1963[141]. However, in 1966 it was reported that upon failing to repeat the earlier results there is no 'adequate basis for further discussion of the species previously observed'[142,143]. Cyclopropanes with



electrophoric[139] substituents (e.g. π-electron systems like carbonyl or aromatic groups) on the other hand, easily accept electrons.

Stable substituted 'cyclopropyl radical anions' have been prepared by Bauld and coworkers[144] and Russell and coworkers[145].

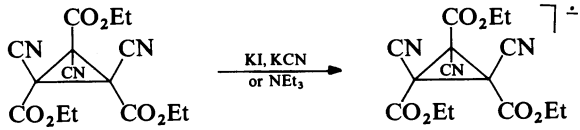


(127$^{\cdot-}$) (128$^{\cdot-}$) (129$^{\cdot-}$)

Most interestingly, reduction of 9-cyclopropylanthracene and 1,4-dicyclopropylnaphthalene led to the planar cyclopropyl conformations in **127**$^{\cdot-}$ and **128**$^{\cdot-}$ as opposed to the normally observed bisected[155] cyclopropyl conformations as, for example, in the cyclopropylsemidione **129**$^{\cdot-}$. In all other cyclopropane derivatives previously studied except **127**$^{\cdot-}$ and **128**$^{\cdot-}$, q_i, the excess charge density present in the relevant p orbital of the electrophore, is zero or positive. Even in semidione radical anion systems q_i is calculated (HMO) to be positive ($\sim +0.10$). Thus it is reasonable to assume that the change in the conformational preference of cyclopropyl may be related to the change in sign of q_i.

The underlying reason could be that the Walsh model of cyclopropane has a quasi-cyclopropenyl ring system which could be more effective at accepting an electron pair than the external p system, which is so adept at electron pair donation. Delocalization into the former one would require the planar conformation observed for the radical anions **127**$^-$ and **128**$^-$.

Another stable cyclopropane radical anion was possibly observed by Papa[146] when he reacted the cyclopropane **130** with nucleophiles such as potassium iodide, potassium cyanide and triethylamine.



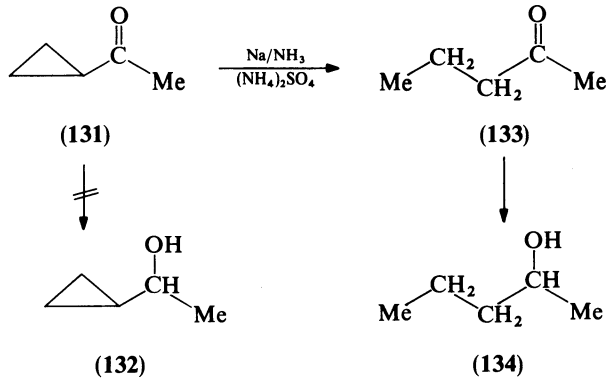
(130) (130$^{\cdot-}$)

An ESR spectrum 'consistent with the cyclopropane structure **130**$^{\cdot-}$' was obtained on electrolytic reduction of **130**. Undoubtedly **130**$^{\cdot-}$, if it has the proposed structure, will owe its stability to the many and excellent electrophoric substituents as this is the case with **127**$^{\cdot-}$, **128**$^{\cdot-}$ and **129**$^{\cdot-}$. The facile ET to **130** from the nucleophiles mentioned is remarkable.

2. *Reductive cleavage of cyclopropanes*

a. Regioselectivity

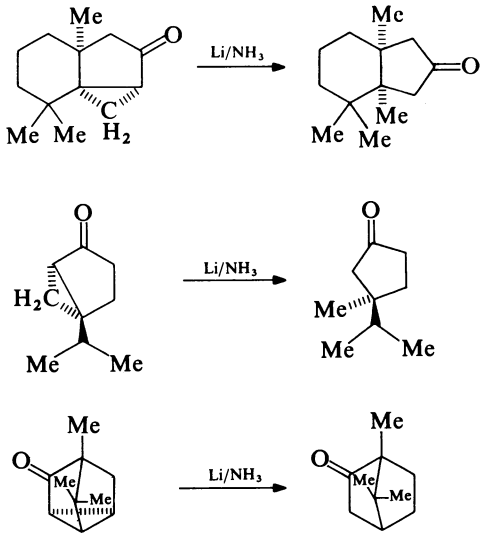
The first report on the reduction of a *carbonyl* substituted cyclopropane was published in 1949[147]. Reactions of methyl cyclopropyl ketone (**131**) with sodium in liquid ammonia in the presence of ammonium sulfate yielded instead of the expected methyl cyclopropylcarbinol (**132**) only a mixture of 2-pentanone (**133**) and 2-pentanol (**134**).



(**131**) (**133**)

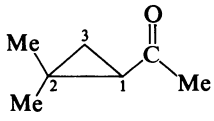
(**132**) (**134**)

Norin[148b] showed in 1965 that the reduction of conjugated cyclopropyl ketones with lithium in liquid ammonia proceeds via a highly stereospecific opening of the three-membered ring. The steric course of the reductions appears to be determined by the configuration of the starting material. The cyclopropane bond which is cleaved is the one possessing maximum overlap of the Walsh orbitals with the π orbital of the carbonyl group, as exemplified by the following transformations.

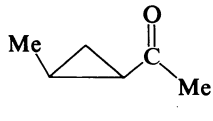


The importance of the geometrical factor in rigid systems was confirmed by Dauben and coworkers[149] who also pointed out that in such systems the process is not controlled by thermodynamic considerations. It is not necessarily the most stable (= least substituted) carbanion which is formed ('electronic factor').

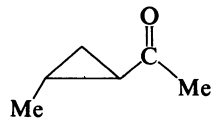
In a further study using the cyclopropyl ketones **135**, *cis*-**136** and *trans*-**136**, in which two bonds of the cyclopropane ring, C(1)–C(2) and C(1)–C(3), are free to overlap with the carbonyl π-system, the importance of electronic versus steric factors was evaluated[149b].



(135)

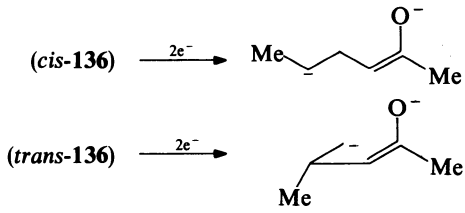


(cis-**136)**



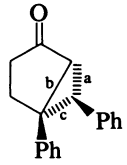
(trans-**136)**

The reduction products that predominate in the reaction mixture from the cleavage of the 2,2-dimethyl-**135** and the *cis*-2-methyl cyclopropyl ketone (*cis*-**136**) arise from C(1)–C(2) bond breaking. In contrast, the *trans*-2-methyl cyclopropyl ketone (*trans*-**136**) fragments at the C(1)–C(3) bond. The observed ring-opening pattern suggests that steric factors can control the direction of cleavage 'presumably through unsymmetrical overlap of the carbonyl π system with one of the cyclopropane bonds'. In the absence of these steric elements as in the case of the *trans*-substituted *trans*-**136** the bond that cleaves is the one

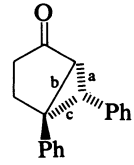


that gives the more thermodynamically stable carbanion intermediate Fraisse-Jullien and Frejaville[150] and House and Blankley[151] arrived at similar conclusions.

Overlap control by steric factors of *phenyl* substituents in cyclopropanes additionally containing a carbonyl group have been described by Zimmerman and coworkers[152] in the liquid ammonia reduction of the isomeric diphenyl cyclopropyl ketones *cis*- and *trans*-**137**.



(cis-**137)**

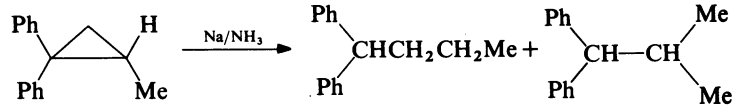


(trans-**137)**

In *cis*-**137**, bond a is more easily broken than bond b; the reverse is true in the case of *trans*-**137**. Interestingly, the reductive degradation of *cis*- and *trans*-**137**, respectively, with Li/NH_3, is related to stereoelectronic control in the photochemical transformations of these compounds.

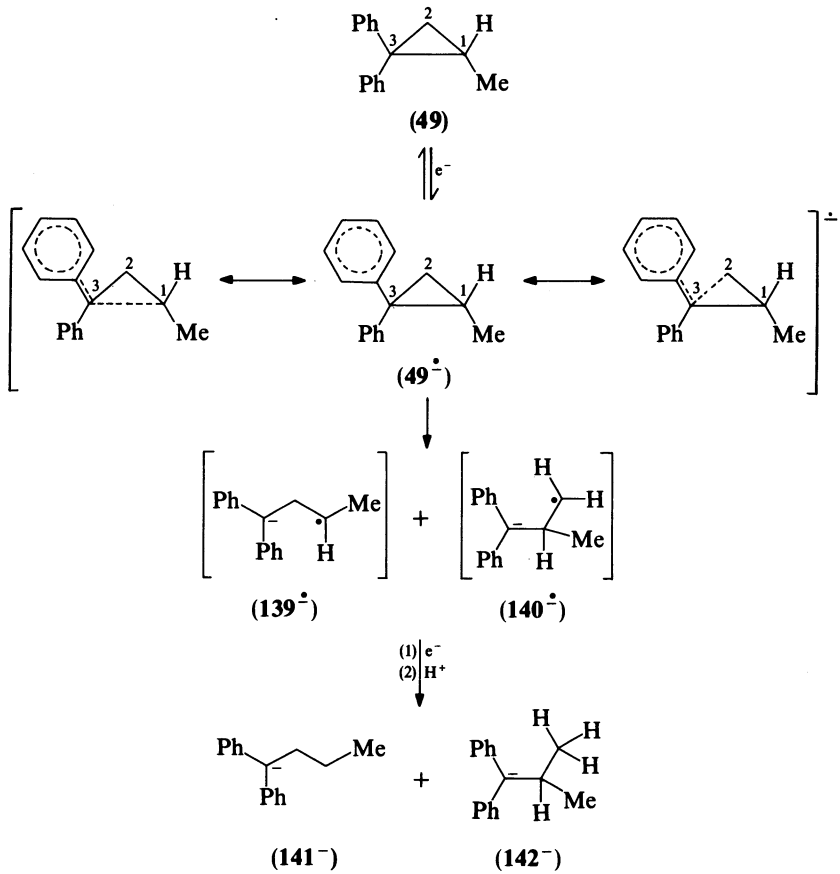
The reduction of 1-methyl-2,2-diphenylcyclopropane **49** and of one of its enantiomers, (+)-(*R*)-**49**, with Na/NH_3 to give 1,1-diphenylbutane (**138**) and 1,1-diphenyl-2-

methylpropane (**123**) in a ~ 5.5:1 ratio over a wide concentration range has been studied by Walborsky and Pierce[153a].



(**49**) (**138**) (**123**)

From the well known ability of phenyl groups to accept electrons from sodium in NH_3[154] the mechanism outlined in Scheme 16 was proposed for the opening of the cyclopropane ring in **49** and other phenyl-substituted cyclopropanes.



SCHEME 16. Proposal for the reduction of 1-methyl-2,2-diphenylcyclopropane **49** and other phenyl-substituted cyclopropanes with sodium in NH_3[153a].

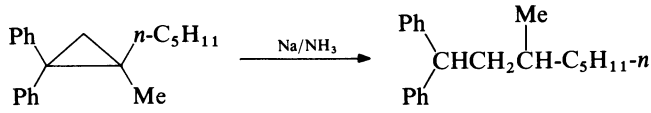
It has been found that at least one phenyl group attached to the cyclopropane ring is a necessary condition for the ring-opening: 2,2-diphenyl- and *trans*-2-phenylcyclopropanecarboxylic acid are opened by Na/NH_3 while 2,2-dimethyl- and cyclopropanecarboxylic acid are not opened[153a].

From these results it is quite understandable that the parent cyclopropyl radical anion is not observable by ESR (*vide supra*), and that ring-opening to give the parent trimethylene radical anion, the parent 1,3-dianion or any follow-up products also does not occur[141-143].

The role of the phenyl group is to accept an initial electron to form the short-lived radical anion **49**$^{\cdot-}$. ESR experiments, however, failed to demonstrate the existence of species such as **49**$^{\cdot-}$, or the trimethylene radical anions **139**$^{\cdot-}$ and **140**$^{\cdot-}$. This means that if **49**$^{\cdot-}$ is formed it must readily open to **139**$^{\cdot-}$ and **140**$^{\cdot-}$ which themselves must quickly add another electron to form a dianion which is protonated by the solvent to give the anions **141**$^-$ and **142**$^-$, respectively.

Moreover, the ring-opening of **49**$^{\cdot-}$ to **139**$^{\cdot-}$ and **140**$^{\cdot-}$ is *irreversible* in the presence of sodium in ammonia since optically active (+)-(*R*)-**49** is recovered without loss of optical activity[153b].

That intermediates such as **139**$^{\cdot-}$, not unexpectedly, would cause loss of optical activity was shown by using (−)-(*R*)-1-*n*-pentyl-1-methyl-2,2-diphenylcyclopropane (**143**) as the starting material. The resulting **144** was completely racemic[153a].

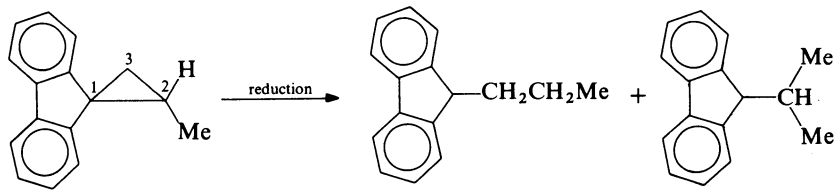


(143) **(144)**

The predominant formation of **138** from **49** via 1,2-bond cleavage of **49**$^{\cdot-}$ to give **139**$^{\cdot-}$ is expected on the basis that the radical anion **139**$^{\cdot-}$ would be predicted to be more stable than the isomeric radical anion **140**$^{\cdot-}$. This argument presumes that there is almost no negative charge on the carbon atom bearing the methyl substituent; otherwise **140**$^{\cdot-}$ should be more stable. This assumption seems reasonable because the negative charge is very well stabilized by two phenyl substituents. Furthermore it seems unlikely that instead of **139**$^{\cdot-}$ and **140**$^{\cdot-}$ the corresponding 1,3-dianions have been formed *directly* from their common cyclopropane dianion precursor. This, however, has not been excluded rigorously by means of these experiments.

Reductions of 1,1-biphenylene-2-methylcyclopropane **119** with Na/NH_3, Na/NH_3/*t*-BuOH, Li/NH_3, electrolysis, Na/glyme and sodium naphthalenide/glyme/25°(−78°C) essentially confirm the results with **49**, although under any conditions a higher ratio of C(1)–C(2) bond cleavage is observed in the case of **119**[153b].

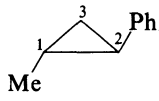
What is the underlying reason? In **119**, the phenyl groups are frozen in the preferred bisected[155] conformation for interaction with the Walsh orbitals of both the C(1)–C(2)



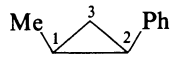
(119) 81–96% : 19–4%

and the C(1)–C(3) bond. Thus electronic considerations are more important than steric ones. Therefore, the direction of the cleavage should even more be determined by the stability of the ring-opened radical anions corresponding to **139**$^{\cdot-}$ and **140**$^{\cdot-}$ which again are believed to be intermediates. This makes sense since a negative charge is more stabilized in a fluorenyl than in a diphenyl methyl anion thus making the fluorenyl trimethylene radical anion, which corresponds to **139**$^{\cdot-}$, even more stable.

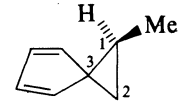
Steric and electronic factors in the reductive cleavage of methyl-substituted phenyl cyclopropanes (**145**) and in spiro[2.4]hepta-4,6-dienes like **146** have been investigated by Staley and Rocchio[156].



(*trans*-**145**)



(*cis*-**145**)



(**146**)

In *trans*-**145** Li/NH_3 reduction cleaved primarily the C(2)–C(3) bond (k(2)–(3)/k(2)–(1) = 360 ± 20) whereas the *cis*-**145** is cleaved in the opposite direction (k(2)–(1)/k(2)–(3) = ~ 70).

The high regioselectivity in the cleavage of *trans*-**145** (in which there is no steric bias for either pathway) shows that a methyl group exerts a destabilizing effect relative to hydrogen for the cleavage. This is consistent with a description of the activated complex in the case of *trans*-**145** with a substantial negative charge also on the cyclopropyl β-carbon of the bond undergoing cleavage.

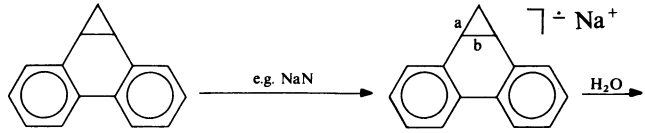
In the case of *cis*-**145** the conformation of maximum overlap for cleavage of bond C(2)–C(3) possesses a substantial steric interaction between the methyl group and the *ortho* hydrogen atom of the phenyl ring. Therefore, the cleavage of C(2)–C(1) is favored.

From the very different reduction products from *cis*- and *trans*-**145**, respectively, with sodium in NH_3 one can conclude that a possible trimethylene radical anion intermediate is not *reversibly* formed. Otherwise, both stereoisomers *cis*- and *trans*-**145** should lead to the same reduction products. An irreversible ring-opening has similarly been observed in the Na/NH_3 reduction of (+)-(*R*)-**49**[153b], as shown earlier. Comparable results to those of *cis*- and *trans*-**145** have been observed with the corresponding cyclopropyl ketones *cis*- and *trans*-**136**[149b] (see above).

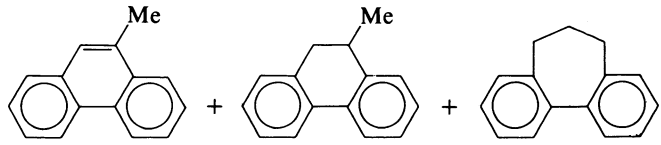
The destabilizing effect of a methyl group relative to hydrogen is also observed in the cleavage of the spiro[2.4]hepta-4,6-diene **146**. Na/NH_3 reduction leads to 1- and 2-*n*-propyl-, and 1- and 2-isopropylcyclopentadienes in a 1 : 4.8 ± 0.3 ratio. Since the rigid **146** does not provide conformational advantage to the breaking of either bond C(3)–C(2) or C(3)–C(1) the moderate preference for the cleavage of C(3)–C(2) indicates a small amount of excess negative charge on the methyl-substituted carbon atom C(1) in the activated complex, in agreement with the negative charge being largely delocalized in the incipient cyclopentadienyl ring. Although the results of **146** are strongly suggestive of radical anion in favor of dianion intermediates it has been pointed out by Staley and Rocchio that one cannot distinguish between these two mechanisms (or a combination thereof) on the basis of the present data[156].

SET reduction of dibenzonorcaradiene (**147**) with lithium, sodium or potassium naphthalenide followed by quenching with water led to 9-methylphenanthrene (**148**) (16–24%), 9-methyl-9,10-dihydrophenanthrene (**149**) (33–43%) and 6,7-dihydro-5-*H*-dibenzo[a,c]cycloheptane (**150**) (23–34%)[139].

The intermediate formation of the radical anion **147**$^{\cdot-}$ is assumed because of the green colour of the solution due to an electrophore which encompasses at least the biphenyl



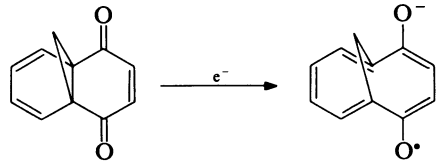
(147) (147$^{\bullet-}$)



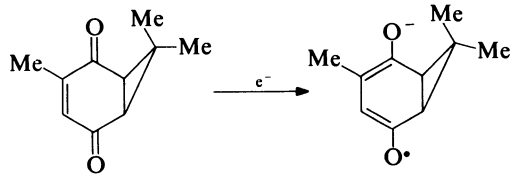
(148) (149) (150)

electrophore. Preferential cleavage of bond a is caused by a stereoelectronic effect: the external cyclopropane bonds are well oriented for overlap with the biphenylene π-system; the internal bond is nearly perpendicular to that system. Why still 23–24 % **150** is formed although the cleavage of bond b is 'an apparent violation of the orbital symmetry prediction' is not quite clear.

Ring-opening, again presumably of the radical anion, is observed in the reduction of **151** to give the radical anion **152**$^{\bullet-}$. Reduction of **153**, in contrast, gives the 'closed' radical anion **153**$^{\bullet-}$[145a].



(151) (152$^{\bullet-}$)

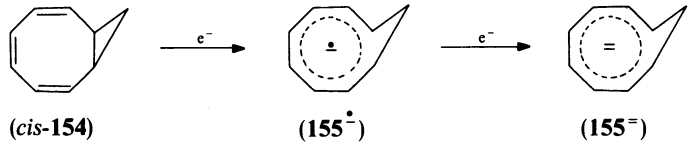


(153) (153$^{\bullet-}$)

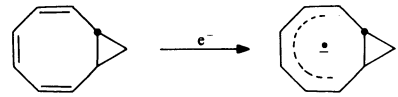
The reduction of *cis*- and *trans*-bicyclo[6.1.0]nona-2,4,6-triene (*cis*- and *trans*-**154**, respectively) under various conditions has been studied by several groups[157,158].

Reduction of *cis*-**154** proceeds through the nine-electron homoaromatic radical anion **155**$^{\bullet-}$ to give the delocalized monohomocyclooctatetraene dianion **155**$^{=}$[157].

In contrast, the bicyclic radical anion *trans*-**154**$^{\bullet-}$ is produced exclusively upon reduction of *trans*-**154** with a potassium mirror in THF or DME solution at −90°C[158]. These observations agree fully with orbital symmetry considerations if the highest occupied MOs of *cis*- and *trans*-**154** are the levels which control reactivity, thus requiring disrotatory bond



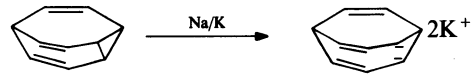
(*cis*-**154**) (**155**$^{\bullet}$) (**155**$^{=}$)



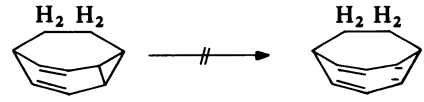
(*trans*-**154**) (*trans*-**154**$^{\bullet}$)

cleavage of the central cyclopropane bond[157d]. Disrotatory ring-opening of *cis*-**154** to give *cis,cis,cis,cis*-cyclononatetraene radical anion (**155**$^{\bullet}$) is accordingly favorable while the analogous reaction channel starting from *trans*-**154** is prohibited by the high-strain energy and poor p-π overlap in the *trans,cis,cis,cis*-cyclononatetraene radical anion. However, the ring-opening process is not as clear if the symmetries of all occupied orbitals in starting material and product(s) are considered. The orbital correlation diagram for disrotatory and conrotatory modes of cyclopropyl ring-opening in *cis*-**154**$^{\bullet}$ show that both processes are formally disallowed as the symmetries of starting material and product are different. However, if one assumes $\beta_{1,8} = 1.0\beta_0$ for the ring-opened product **155**$^{=}$, a disrotatory mode is allowed for the dianion. Thus it is possible that the *dianion* undergoes ring-opening. Again, we are confronted with the unsolved question which species opens the ring.

Reaction of bullvalene (**156**)[159a] with Na/K alloy in THF or DME at room temperature led to the bicyclo[3.3.2]decatrienyl dianion **157**$^{=}$ **2K**$^{+}$.



(**156**) (**157**$^{=}$ **2K**$^{+}$)

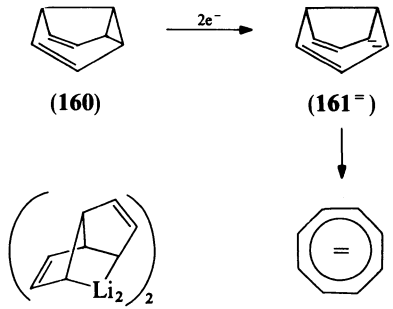


(**158**) (**159**$^{=}$)

The lithium salt was accessible by LiBr metathesis. The facile formation of **157**$^{=}$ **2K**$^{+}$ in contrast to the unsuccessful reduction of dihydrobullvalene (**158**) which does not give the corresponding dianion **159**$^{=}$, has been discussed along the lines of longicyclic stabilization of **157**$^{=}$ as opposed to the bishomoantiaromatic nature of the bicyclo[3.3.2]decadienyl dianion **159**$^{=}$. The value of such qualitative theoretical argument has increasingly been questioned in recent years, and particularly as it applies to anions. A literature survey of such criticism is given in Ref. 159b.

Reduction of semibullvalene (**160**) should lead to the destabilized [3.3.0]dianion **161**$^{=}$. A symmetry-allowed and thermodynamically attractive isomerization to the cyclooctatet-

raenyl dianion **162**$^{=}$ would be difficult to resist. Treatment of **160** with lithium in THF or dimethyl ether even at $-78°C$ leads to 'dilithium semibullvalenid' which actually exists as the C_{2h} and D_2 diastereoisomers of bis(bicyclo[3.3.0]octa-3,7-diene-2,6-dyil)tetralithium (**163**), the first structurally characterized pair of diastereoisomeric organolithium

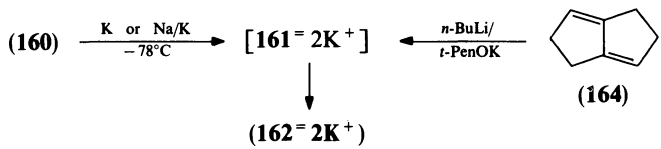


(**160**) (**161**$^{=}$)

(**163**) (**162**$^{=}$)

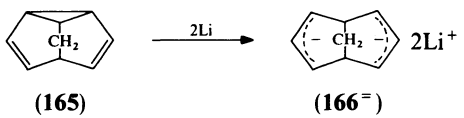
compounds[159b–d, 160]. 'Dilithium semibullvalenid' (**163**), as expected, isomerizes at 0°C with an apparent first-order rate constant $k = 9.0(1) \cdot 10^{-5}\,s^{-1}$ to **162** $2Li^{+}$.

The potassium species **161**$^{=}$ $2K^{+}$ could not be prepared by deprotonation of a mixture of tetrahydropentalenes (e.g. **164**) with a 1:1 *n*-butyllithium/potassium *t*-pentoxide mixture[161].

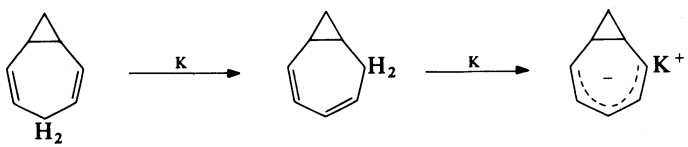


Instead, the dipotassium salt of the cyclooctatetraenyl dianion **162**$^{=}$ $2K^{+}$ was detected exclusively. This result was confirmed by Goldstein and Wenzel[159c]: reduction of semibullvalene (**160**) with potassium or sodium/potassium alloy even at $-78°C$ resulted only in **162**$^{=}$ $2K^{+}$.

Müllen and coworkers[160b] were able to transform barbaralane (**165**) with lithium into the dianion **166**$^{=}$. In the presence of potassium, 3,4-homotropilidene (**167**), in contrast, first isomerizes to **168** which then deprotonates to give the monoanion **169**$^{-}$. Interestingly, the three-membered ring is not cleaved in that case. In all these cases it is not clear which species opens the ring.



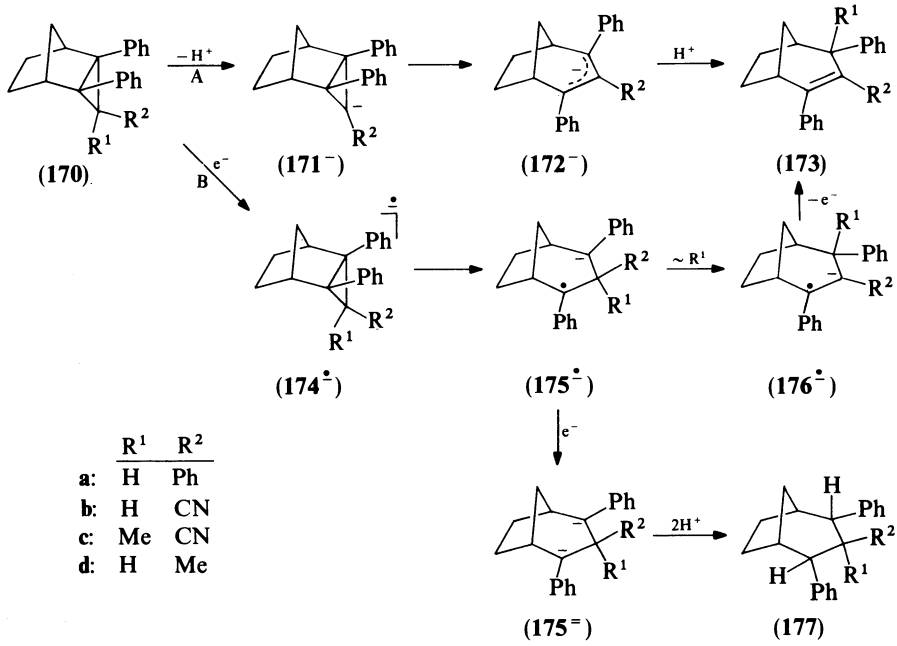
(**165**) (**166**$^{=}$)



(**167**) (**168**) (**169**$^{-}$)

In the following examples ET reactions to cyclopropanes have been presumed to account for the observed cyclopropane → propene isomerizations.

2,3,4-Triphenyl-*endo*-tricyclo[3.2.1.$0^{2,4}$]octane (**170a**) isomerizes in the presence of base, e.g. *t*-BuOK in DMSO (70°C, 20 h), to 2,3,4-triphenylbicyclo[3.2.1]oct-2-ene (**173a**) (Scheme 17). Originally this was proposed by Mulvaney and coworkers[162] to occur via forbidden disrotatory ring-opening of the cyclopropyl anion **171a**$^-$ to give the allyl anion **172a**$^-$ which is then protonated to give **173a** (pathway A).



	R^1	R^2
a:	H	Ph
b:	H	CN
c:	Me	CN
d:	H	Me

SCHEME 17. Reactions of *endo*-tricyclo[3.2.1.$0^{2,4}$] octanes with base and ET reagents (gegenions omitted)

It was concluded later[163] that 'the reaction of **170a** with *t*-BuOK in DMSO or HMPA (25°C, 24 h), or with dimsyl potassium in DMSO (70°C, 24 h) appears to proceed by a radical pathway'. The authors proposed that an initial SET from base to **170a** affords radical anion **174a**$^{\bullet-}$ which opens to **175a**$^{\bullet-}$. The latter was envisaged to rearrange to **176a**$^{\bullet-}$ which loses an electron 'possibly to **170a**', to give **173a** (pathway B).

In order to shed some more light on the mechanism of this isomerization reaction Boche and Marsch[164] investigated the reactions of the *endo*-bicyclo[3.2.1.$0^{2,4}$]octanes **170a–d** with different bases and ET reagents, respectively. It was shown that the cyclopropyl anion **171b**$^-$, transforms completely and in a disrotatory manner into the allyl anion **172b**$^-$, even at −75°C within 1 h, which strongly suggests a similar pathway in the case of **170a** with base. Further support is provided by the reaction of **170a** with the 'superbase' potassium 3-aminopropylamide (KAPA) in 1,3-diaminopropane[165]: **170a** is completely transformed into **173a** after 1 h at 0°C. In the reaction of 2,3,4-triphenyl-*endo*-tricyclo[3.2.1.$0^{2,4}$]octene with lithium 2-aminoethylamide in ethylenediamine at 100°C a similar cyclopropyl/allyl anion pathway has been formulated by Martin[166].

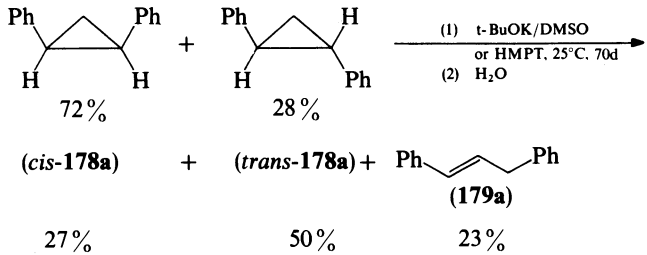
A totally different picture emerges if **170c** and **170d** are used (Scheme 17). Treatment of the methylcyanocyclopropane **170c** with base (LDA, THF, −75°C, 1 h; *t*-BuOK, DMSO,

25°C, 24 h; *t*-BuOK, DMSO, 70°C, 5 h) leads to complete recovery of starting material. **170d** is also unreactive towards base (*t*-BuOK, DMSO, 70°C, 6 h; KAPA, 1,3-diaminopropane, 25°C, 24 h). Thus replacing the acidic H-3 in **170b** by a methyl group as in **170c** or making it comparatively non-acidic as in **170d**, prevents deprotonation and therefore does not lead to a reaction with base although the proposed[163] SET reaction still could occur. With a real SET reagent (Na/K alloy, THF) **170d** is transformed into **177d** in a manner analogous to the transformation of **170a** to **177a** by sodium naphthalenide, followed by protonation[163].

The behavior of **170c** and **170d** therefore supported the cyclopropyl anion pathway A in favor of the ET mechanism B. Furthermore, as far as the proposed rearrangement of the proposed radical anions $\mathbf{175}^{\cdot-} \rightarrow \mathbf{176}^{\cdot-}$ is concerned, it is shown later in this section that in similar trimethylene radical anions such rearrangements do not take place.

One can therefore conclude that the base-catalyzed cyclopropane → propene isomerization **170a** → **173a** is induced by an acid–base and not by an ET reaction.

It is also rather doubtful whether the reaction of a 72:28 mixture of *cis*- and *trans*-1,2-diphenylcyclopropane (**178a**) with *t*-BuOK in DMSO or in HMPA at 25°C for 70 days leading, i.e., to 23% 1,3-diphenylpropene (**179a**) is caused by electron transfer[163].



The authors of this work[167] at least suggested that 'further investigation is required to determine the mechanism of the described reaction'.

b. Electron transfer catalyzed stereoisomerization

Electron transfer reactions to various cyclopropanes with special concern for the question of the formation of radical anion intermediates and their chemistry have been studied by Boche and coworkers[168]. A typical example is given by the reaction of *cis*-1,2-diphenylcyclopropane (*cis*-**178a**) with Na/K alloy at 0°C to yield on protonation *trans*-1,2-diphenylcyclopropane (*trans*-**178a**), *trans*-1,3-diphenylpropene (*trans*-**179a**, together with some *cis*-**179a**), and 1,3-diphenylpropane (**181a**). The time-dependent amounts of *cis*-**178a**, *trans*-**178a**, *trans*(+*cis*)-**179a** and **181a** are shown in Table 23.

Table 23 can be summarized as follows:

(1) The cyclopropane *cis*-**178a** disappears steadily; after 40 min nothing is left.

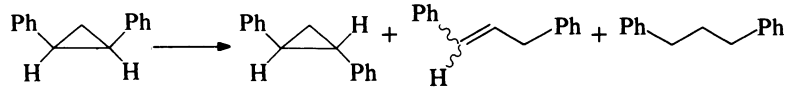
(2) The concentrations of the stereoisomeric cyclopropane *trans*-**178a** and of the propane **181a** pass through a maximum. This demonstrates the intermediacy of *trans*-**178a** and of the 1,3-dianion $\mathbf{180a}^{=}$; $\mathbf{180a}^{=}$ gives the propane **181a** on protonation, as confirmed by deuteration (Scheme 18).

(3) The concentration of the propene **179a** resulting from protonation of the allyl anion $\mathbf{182a}^{-}$ increases steadily.

Similar results have been observed when the reaction was started with the thermodynamically more stable *trans*-cyclopropane *trans*-**178a**, and at different temperatures. Obviously, two different reactions take place:

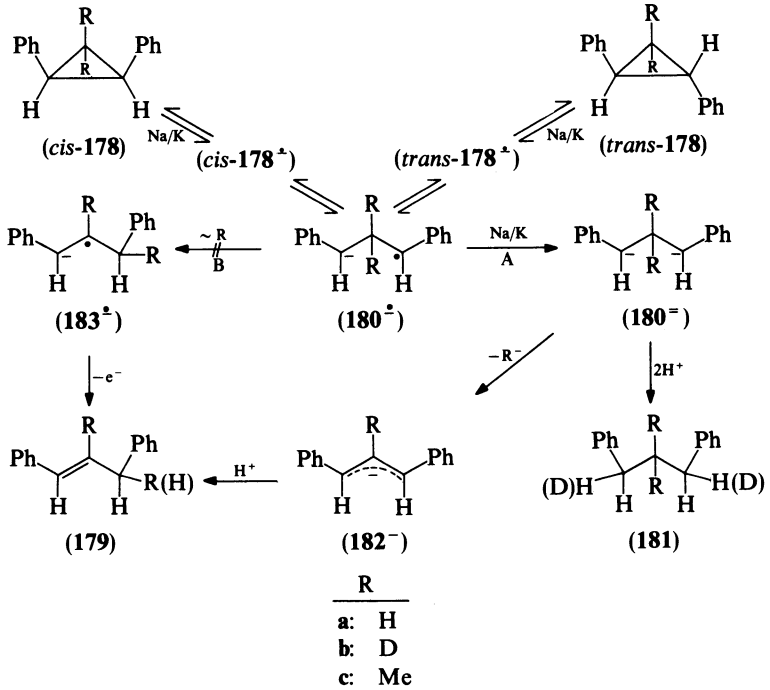
(1) the *stereoisomerization* of the cyclopropanes *cis*-**178** and *trans*-**178**, and
(2) the transformation of the cyclopropanes *cis*- and *trans*-**178** into the *ring-opened products* **179** and **181**.

TABLE 23. Time-dependent yields of *cis*-**178a**, *trans*-**187a**, *trans*(+*cis*)-**179a** and **181a** in the reaction of *cis*-**178a** with Na/K alloy in THF at 0°C, followed by protonation with water



(*cis*-**178a**)	(*trans*-**178a**)	(*trans*(+*cis*)-**179a**)	(**181a**)

Time (min)		Yield %		
0	95	5	—	—
10	83	5	—	12
45	8	57	5	30
120	1	28	30	41
240	—	9	53	38

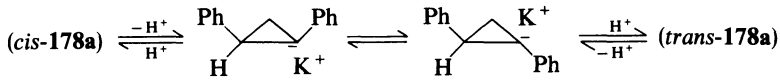


SCHEME 18. *Cis/trans* isomerization of the *cis*- and *trans*-1,2-diphenylcyclopropanes (*cis*- and *trans*-**178a–c**) and formation of the 1,3-diphenylpropanes (**181a–c**) and 1,3-diphenylpropenes (**179a,b**) with Na/K in THF (gegenions omitted).

The suggestion that the *stereoisomerization* is an *ET-catalyzed* reaction occurring via the stereoisomeric trimethylene radical anions **180**$^{\cdot-}$ (Scheme 18) is confirmed by the following three results:

(1) The *thermal* isomerization *cis*-**178a** → *trans*-**178a**, having a rate constant $k = \sim 10^{-4}\ s^{-1}$ at 200°C, as measured by Rodewald and DePuy[169], extrapolates to a half-life at 0°C of $\sim 10^9$ years. Clearly, the observed reaction in the presence of Na/K is not a thermal one: *cis*-**178a** has disappeared completely after 40 min.

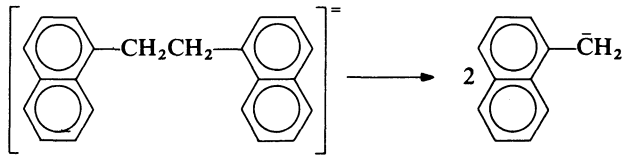
(2) The *cis–trans* isomerization in the case of the 1,2-diphenylcyclopropanes **178a** in the presence of Na/K is not a *base-catalyzed* reaction with the cyclopropyl anions **183**$^-$ as

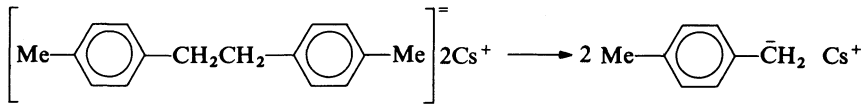


(**183**$^-$)

intermediates. This is nicely shown by the work mentioned in the previous section: *cis*-**178a**, in the presence of *t*-BuOK in DMSO or HMPA, isomerizes to *trans*-**178a** even within 70 days at 25°C only slightly[167].

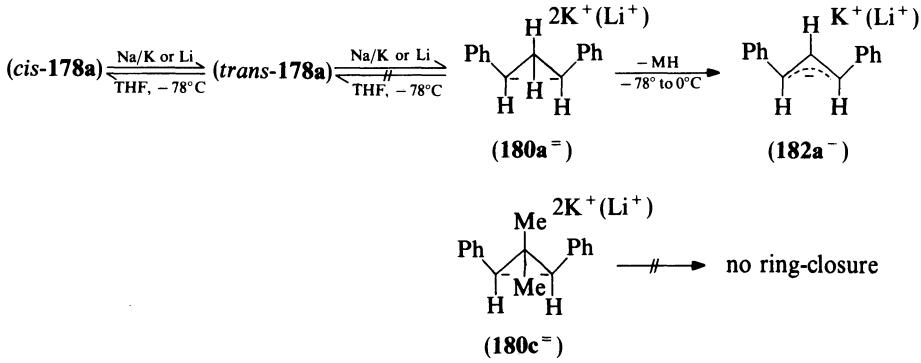
(3) The stereoisomerization of the cyclopropanes **178** via 'dianions' **180**$^=$ (Scheme 18) is also rigorously excluded. *A priori*, this is not a totally unlikely pathway since Lagendijk and Szwarc[170] have deduced from kinetics that it is the dianion that breaks the C–C bond in the reaction of electron sources with 1,2-di-α-naphthylethane to give α-naphthylmethyl anions. Similarly, Grovenstein and coworkers[171] have recently found that bond cleavage in the reaction of 1,2-di-*p*-tolylethane with Cs/K/Na alloy occurs at the dianion stage.





The formation of the 1,3-dianions **180**$^=$ from the corresponding cyclopropane dianions would correspond exactly to these reactions. If the dianions **180**$^=$ were intermediates in the ET-catalyzed stereoisomerization of the cyclopropanes the *reverse reaction*—formation of the cyclopropanes **178** from the dianions **180**$^=$—should also take place. Preparation of the 1,3-dianion **180a**$^=$ **2K**$^+$(**Li**$^+$) from the cyclopropane *cis*-**178a** with Na/K alloy or with lithium at −78°C shows clearly that **180a**$^=$ **2K**$^+$ (**Li**$^+$) is stable at −78°C (Scheme 19).

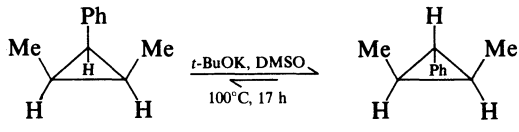
Whether this is also the case at 0°C cannot be decided with **180a**$^=$ [172] because it loses hydride between −78° and 0°C to give the allyl anion **182a**$^-$. If the methylene hydrogens in **180a**$^=$ are replaced by two methyl groups as in **180c**$^=$ then elimination does not take place. **180c**$^=$ is stable up to 0°C; importantly, ring-closure to give *cis*- or *trans*-**178c** is not observed! The corresponding cyclopropanes *cis*- and *trans*-**178c**, however, isomerize in the presence of Na/K alloy.



SCHEME 19. 1,3-Dianions are not intermediates in the ET-catalyzed isomerization of cyclopropanes

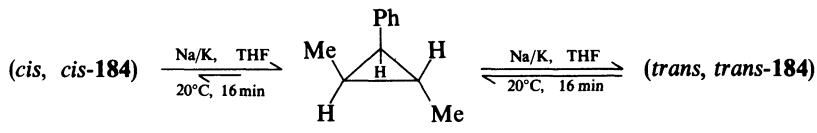
The difference between a *base-catalyzed* and an *ET-catalyzed cis/trans*-isomerization of cyclopropanes is also nicely demonstrated by the following example.

The *base-catalyzed* *t*-BuOK, DMSO, 100°C, 17 h isomerization of *r*-1-phenyl-*c*-2, *c*-3-dimethyl- and *r*-1-phenyl-*t*-2-, *t*-3-dimethylcyclopropane (*cis,cis*-**184** and *trans,trans*-**184**), as studied by Closs and Moss[173], and the ET-catalyzed (Na/K, THF, 20°C, 16 min) reaction of these cyclopropanes are shown below.



(*cis, cis*-**184**) (*trans, trans*-**184**)

1 99

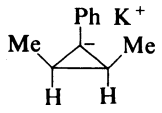


(*cis, trans*-**184**)

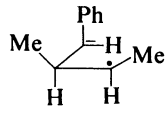
1 44 55

It is not only the conditions of temperature and time which are totally different in these two reactions. In the *base-catalyzed* reaction only *cis,cis*- and *trans,trans*-**184** are formed as expected if the cyclopropyl anion **185**$^-$ is the intermediate.

In the much faster ET-catalyzed reaction a new stereoisomer, *r*-phenyl-*c*-2,*t*-3-dimethylcyclopropane (*cis,trans*-**184**) shows up in equilibrium with the isomers *cis,cis*- and *trans, trans*-**184**. This excludes the possibility that the cyclopropyl anion pathway occurs exclusively. It also excludes the belief that under base-catalyzed conditions ET-catalyzed isomerizations must play a significant role. This result also supports the conclusion[164] that in the base-catalyzed reaction of **170a** the proposed ET mechanism[163] is not valid (see



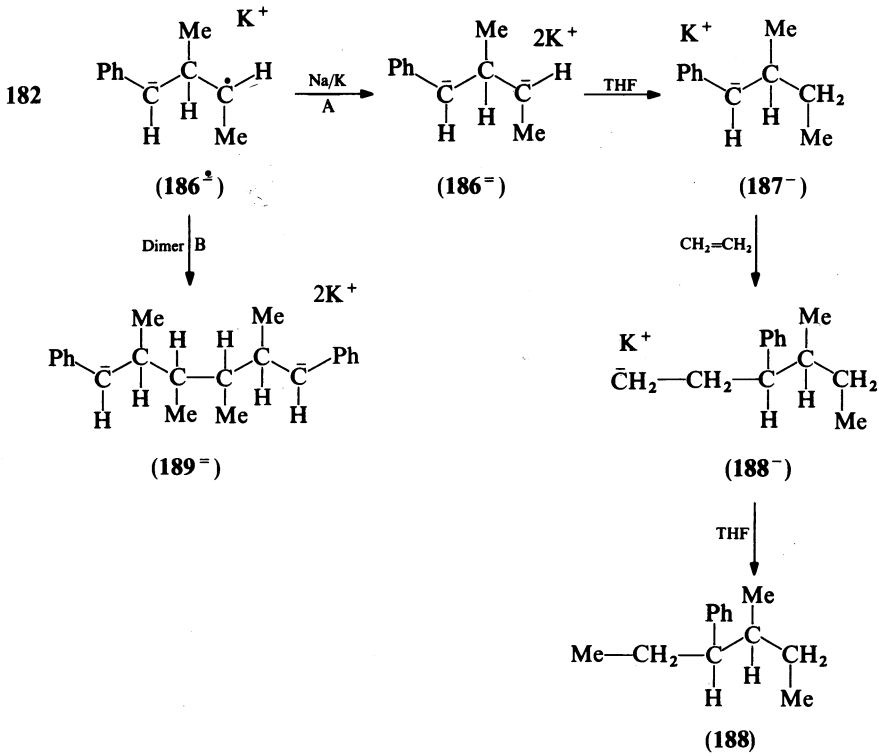
(185⁻)



(186·⁻)

previous section). The formation of *cis,trans*-**184** requires that in the course of the equilibration a cyclopropane bond is broken. As in the case of stereoisomerization of the 1,3-diphenylcyclopropanes **178** with Na/K alloy a trimethylene radical anion, here **186**·⁻, should be an intermediate.

That **186**·⁻ indeed is an intermediate is shown by a prolonged reaction of the equilibrium mixture of the cyclopropanes **184** with Na/K. After 60 h at 20°C the following reactions have been observed (Scheme 20).



SCHEME 20. Reactions of the trimethylene radical anion **186**·⁻ after 60 h at 20°C, followed by workup with water

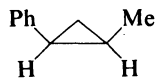
Pathway A: **186**·⁻ is further reduced to the dianion **186**⁼ which is immediately protonated by THF to give the benzylic anion **187**⁻. The ethylene formed on decomposition of THF reacts with some **187**⁻ to give **188**⁻ which is also protonated by

THF to give **188** in 47% yield. On workup with water protonated $\mathbf{187}^-$ is formed and isolated in 16% yield.

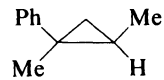
Pathway B: more importantly, the dimer $\mathbf{189}^=$ of the radical anion $\mathbf{186}^{\cdot-}$ is also formed. Protonation with water leads to the corresponding hydrocarbon **189** in 37% yield.

In summary, the results shown leave no doubt that the reversible stereoisomerizations of the cyclopropanes **178a**, **178c** and **184** in the presence of alkali metals in THF occur via trimethylene radical anions like $\mathbf{180}^{\cdot-}$ and $\mathbf{186}^{\cdot-}$. These ET-catalyzed reactions do not occur in a thermal or base-catalyzed process or via 1,3-dianion intermediates and they differ greatly from the *irreversible* electron transfer reactions with sodium in NH_3, as observed with (+)-(*R*)-**49**[153b] and with the *cis,trans*-isomeric cyclopropanes **145**[156] because of the very fast protonation steps in NH_3. Undoubtedly, however, in the later cases, as strongly suggested by the regioselectivity of the bond cleavages (*vide supra*) trimethylene radical anions are also intermediates. Spectroscopic evidence for a trimethylene radical anion is not available to date.

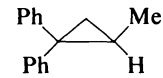
Other reversible ET-catalyzed stereoisomerizations of cyclopropanes have been observed with *cis*-1-methyl-2-phenyl-, *r*-1-phenyl-1-methyl-*c*-2-methyl- and optically active 1-methyl-2,2-diphenylcyclopropane (**190**, **191** and (+)-(*R*)-**49**, respectively)[168a]. Experimental evidence for the existence of intermediate cyclopropane radical anions like *cis*- or *trans*-$\mathbf{178}^{\cdot-}$ (Scheme 18) has not been found in the course of these investigations.



(**190**)

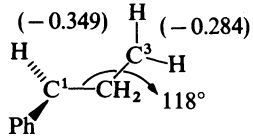


(**191**)

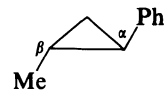


((+)-(*R*)-**49**)

A simple MNDO calculation of the phenyltrimethylene radical anion $\mathbf{192}^{\cdot-}$[174] is in good agreement with experimental results reported by Staley and Rocchio[156]: not only C(1) which bears the phenyl group, but also C(3) has an appreciable amount of



($\mathbf{192}^{\cdot-}$)



(*trans*-**145**)

negative charge. They reported that the 'activated complex' in ET reactions of *trans*-**145** has a substantial negative charge also on the cyclopropyl β-carbon atom of the bond undergoing cleavage.

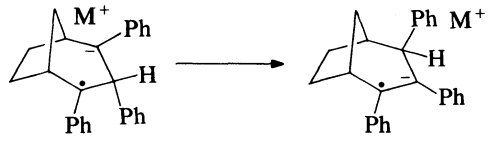
c. Mechanism of formation of isomeric acyclic olefins

In Section III.C.2.b. above clear evidence has been presented that the trimethylene radical anions $\mathbf{180}^{\cdot-}$ are intermediates in the stereoisomerization of the cyclopropanes **178** under ET catalysis (see also Scheme 18). This is also true for other cyclopropanes.

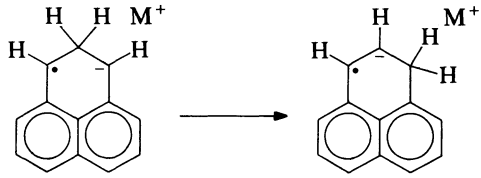
The formation of the *ring-opened* propene (**179**) and propane (**181**) also seems straightforward from Scheme 18, pathway A: the trimethylene radical anion $\mathbf{180}^{\cdot-}$ is further reduced to the dianion $\mathbf{180}^=$ which, as a function of time (Table 23), loses β-hydride H^- (if the β-carbon atom bears hydrogen atoms); protonation of the reaction mixture gives propene (**179**) and propane (**181**). Thus, the structural isomer propene (**179**) *does not result from an ET-catalyzed rearrangement reaction* (pathway B in Scheme 18)!

The literature offers an alternative pathway for the formation of propenes from cyclopropanes in the presence of electron sources as mentioned earlier: rearrangement of the trimethylene radical anion **175a**$^{\dot{-}}$ to give **176a**$^{\dot{-}}$ is the important step, see also pathway B, Scheme 17[163].

A similar rearrangement has been proposed to occur in the trimethylene radical anion **193**$^{\dot{-}}$ to give **194**$^{\dot{-}}$[175].



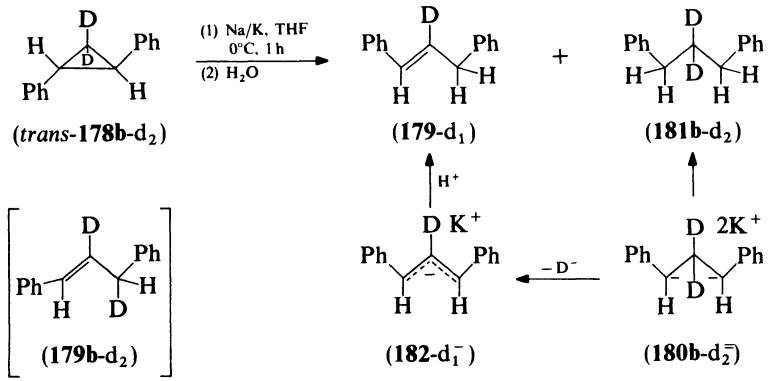
(**175a**$^{\dot{-}}$) (**176a**$^{\dot{-}}$)



(**193**$^{\dot{-}}$) (**194**$^{\dot{-}}$)

Although the radical anion pathway requiring the rearrangement of **175a**$^{\dot{-}}$ to give **176a**$^{\dot{-}}$ is rather unlikely on the basis of the experimental results presented earlier in Section III.C.2.a, this alternative ET-catalyzed route to yield propenes from cyclopropanes via *migration of an atom or a group* has been checked with the cyclopropanes **178**[168b].

When the bis-deuterated cyclopropane *trans*-**178b**-d_2 was reacted with Na/K in THF at 0°C one observed on protonation after 1 h besides 16% *trans*-**178b**-d_2, 6% propene **179**-d_1 and 78% propane **181b**-d_2.



(*trans*-**178b**-d_2) (**179**-d_1) (**181b**-d_2)

(**179b**-d_2) (**182**-d_1^-) (**180b**-$d_2^{=}$)

It is thus unambiguously clear that the propene **179**-d_1 is formed exclusively from the dianion **180b**-$d_2^{=}$ by loss of D^- to give the allyl anion **182**-d_1^-, followed by protonation. This route corresponds to pathway A in Scheme 18. Pathway B in Scheme 18, the proposed alternative[163, 175], which in the case of *trans*-**178b**-d_2 should lead to the bis-deuterated propene **179b**-d_2, is not a viable process. This is in agreement with the general observation that the *intra*molecular 1,2-migration of hydrogen (deuterium) is not a facile reaction in either radicals[176] or carbanions[177].

Finally, it should be noted that geometrical and structural isomerizations of substituted cyclopropanes by means of ET-catalyzed reactions, via intermediate trimethylene radical anions, is only one pathway to perform these reactions. Other possibilites are the thermal reaction via trimethylenes[178], the light induced reaction [179], the photosensitized reaction via trimethylene radical cations[180], the Pd/C-catalyzed reaction[181], and the base-catalyzed reaction[167, 173].

IV. ANIONS

A. Introduction

Cyclopropyl anions have a high synthetic potential, see Section IV.D. Their direct preparation from cyclopropyl halides with metals, by halogen–metal exchange as well as by alkali metal naphthalenide has been discussed in Section III.

In the following sections we concentrate on structural aspects of the cyclopropyl anion and of substituted cyclopropyl anions. Since the structure of these anions and the acidity of the corresponding cyclopropanes correlate intimately with each other, it is inevitable to combine these two subjects in a discussion of cyclopropyl anions and their structure.

B. Formation from Cyclopropane and its Stereochemistry

Theoretical calculations[3, 183, 185a, c] and a variety of experimental results indicate rather early that the hybridization of the C–H bonds in cyclopropane is not sp^3 but rather $sp^{2.28}$ which due to the greater s character, should increase their acidity[182]. However, it wasn't until 1969[184] that the (kinetic) acidity of cyclopropane was finally measured by using cesium cyclohexylamide in *N*-tritiated cyclohexylamine and it was shown that the exchange rate of cyclopropane is $7.0 \pm 0.9 \times 10^4$ faster than that of cyclohexane (Table 24).

TABLE 24. Kinetic acidities of cyclopropane and cyclohexane toward cesium cyclohexylamide at 50°C[184]

	Rel. rate	$J(^{13}C–H)$
Cyclopropane	$7.0 \pm 0.9 \times 10^4$	161
Cyclohexane	1.00	123

The linear correlation[184] between the log of the relative rates and the coupling constants $J(^{13}C–H)$, which is 161 Hz in the case of cyclopropane and 123 Hz in the case of cyclohexane, supports the thesis that the dominant factor in cyclopropane acidity is the amount of s character in the exocyclic C–H bonds.

Accurate anion proton affinities are now available from theoretical calculations[185a] and this enables one to estimate the proton affinity as well as the relative energy of hypothetical carbanion configurations, as, for example, the cyclopropyl anion in the pyramidal C_s and the planar C_{2v} configuration.

	MP2/4-31 + *G*//4-31 + *G* (Hartrees)	Rel. energy (kcal mol^{-1})
Cyclopropyl anion, C_s	−116.48368	0.0
Cyclopropyl anion, C_{2v}	−116.45966	15.1

The 15.1 kcal mol^{-1} higher stability of the pyramidal C_s configuration is in agreement with the experimental results given in detail in Sections III.B.1 and III.B.2. on the

configuration and the configurational stability of various cyclopropyl metal compounds.

An X-ray crystal structure determination of di-μ_3-bromo-di-μ_3-cyclopropyl-tetralithio-tetrabis (diethyl ether) [2LiBr·2*c*-C_3H_5Li·4$(C_2H_5)_2O$] published by Schmidbaur and coworkers[185b] shows nicely the pyramidal configuration of the anionic carbon atom, in agreement with the calculations. The cyclopropyl anion in the gas phase has been studied by Sguires and coworkers[185c].

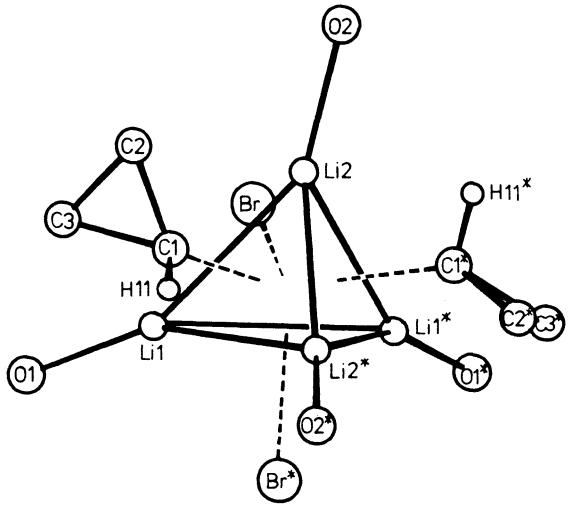
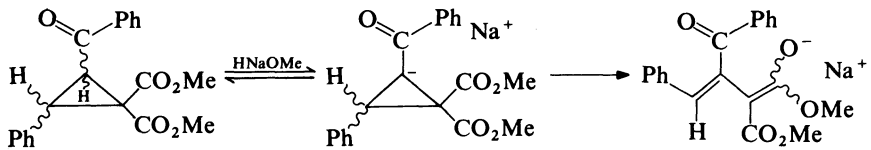


FIGURE 4. Solid state structure of [2LiBr·2*c*-C_3H_5Li·4$(C_2H_5)_2O$][185b].

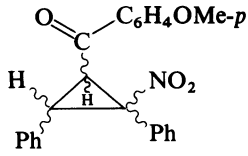
1. *Effect of substituent*

a. α-Carbonyl and α-carboalkoxyl

The chemistry of cyclopropanes substituted with C(O)R groups goes back to the turn of the century. Kohler and his group studied the reaction of the cyclopropane **195** with sodium methoxide which eventually leads[186a] to the formation of **197**.



It was Smith and Showell[187] who inferred that **195** is deprotonated to give the cyclopropyl anion **196** which isomerizes to the allyl anion **197** (the cyclopropyl ⇌ allyl anion rearrangement is treated in detail in Section IV.C.).



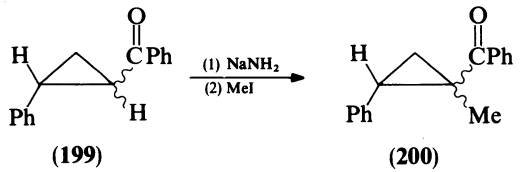
(198)

Similar behaviour has been observed by Kohler and Allen[186b] and by Smith and Showell[187] on treating the tertiary nitrocyclopropyl ketone **198** with a base. Base catalyzed stereoisomerizations of ketones like **198** had also been observed by Kohler and Smith[186c] and by Smith and Showell[187] and were in agreement with the deprotonation of such cyclopropanes to the corresponding cyclopropyl anions. It thus did not seem as if the deprotonation of C(O)R-substituted cyclopropanes would cause any problems.

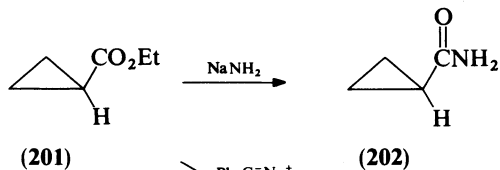
This conclusion had to be revised when Piehl and Brown[188] showed that although they were able to repeat Haller's work on the alkylation of phenylcyclopropyl ketone (**199**) by means of sodium amide and methyl iodide to give **200**[189] (a reaction which they thought was wrong), unexpected reactions occurred in the case of ethyl cyclopropanecarboxylate (**201**). With sodium amide the amide (**202**), and with triphenylmethyl sodium the ketone (**203**) is formed. The latter reaction is normally typical of esters having no α-hydrogen atom!

Piehl and Brown[188] concluded 'that α-hydrogens in *monofunctional* derivatives of cyclopropane are relatively unreactive in accordance with I-strain theory[7] because deprotonation of α to an electron-accepting group should lead to additional strain in exocyclic double-bonded forms', as in the case of the ester enolate of **201**.

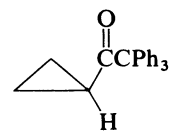
The comparatively low acidity of monofunctional C(O)R-substituted cyclopropanes has been repeatedly confirmed in the literature as shown by the following examples.



(199) (200)

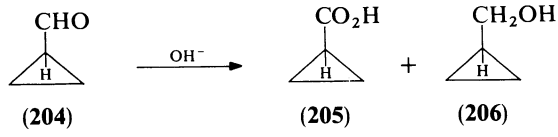


(201) (202)

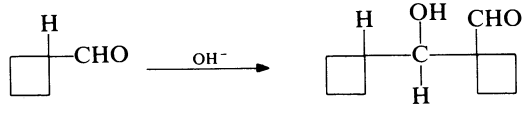


(203)

For *cyclopropanecarboxaldehydes* de Boer and coworkers[190, 191] have investigated the base-catalyzed reaction of the parent compound **204** and compared its acidity with that of the cyclobutanecarboxaldehyde **207**.



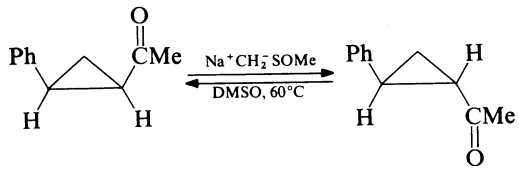
(204) (205) (206)



(207) (208)

In the case of the cyclopropanecarboxaldehyde (**204**) only the Cannizzaro products **205** and **206** were formed. Thus, **204** behaves as if it had no α-hydrogen atom—like the ester **201**. In contrast, in the case of the cyclobutanecarboxaldehyde (**207**), as expected, the normal aldol condensation is much faster, leading to **208** (under the reaction conditions **208** was not actually isolated; instead the Cannizzaro products of this tertiary aldehyde were obtained in 90% yield).

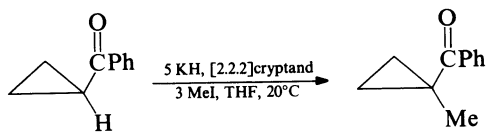
More investigations have been performed with *cyclopropyl ketones*. The isomerization of the *cis*-cyclopropyl ketone **209** to its *trans* isomer **210** was only achieved by means of the rather basic dimsyl sodium in dimethyl sulfoxide at 60°C[192a]. Similarly, esters of cyclopropane carboxylic acids have been isomerized[192b].



(209) (210)

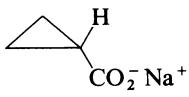
The relative acidities of the α-hydrogens in **209** and **210** have been determined by Itoh and coworkers[193]. In the *cis* compound **209** the hydrogen is exchanged faster than in the *trans* species **210** by a factor of 100. From these and other results it is concluded that the cyclopropyl anion derived from **209** is more stable than that which results on deprotonation of **210**. This has been confirmed by CNDO/2 calculations, however, there is no obvious explanation available. It is also noteworthy that the H/D-exchange in **209** is faster than the base-catalyzed isomerization to give **210**.

Another successful alkylation of a cyclopropyl ketone was reported by Handel and coworkers[194a] when they reacted cyclopropyl phenyl ketone (**211**) with excess potassium hydride (5 M equivalents) in the presence of [2.2.2]cryptand: methylation with methyl iodide gave **212** in 90% yield. The conditions are crucial: without the cryptand, **211** is reduced to the corresponding secondary alcohol in 82% yield.



(211) (212)

As far as *salts of cyclopropanecarboxylic acids* are concerned 'exceedingly low rates' for the deuterium oxide catalyzed H/D exchange have been observed by Bottini and Davidson[195] in the case of the sodium salts **213**, **214** and **215**.



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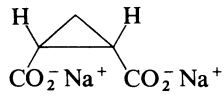

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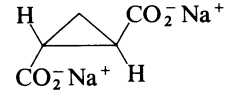
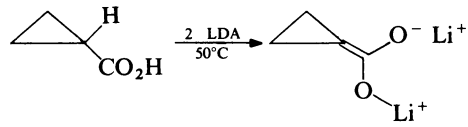


(215)

After 100 h at 152 ± 2°C (> 0.2 N NaOD), exchange of the α-hydrogens was to the extent of 0 ± 16% (**213**), 3 ± 4% (**214**) and 4 ± 4% (**215**).

In agreement with these results Krapcho and Jahngen's[196] attempts to utilize cyclopropanecarboxylic acid (**216**) in the reactions of α-anions of cycloalkanecarboxylic acid salts with cycloalkanones have been unsuccessful.



(216) **(217)**

No condensation products have been isolated and upon quenching with D_2O the starting material **216** was recovered in 25% yield showing no incorporation of deuterium. The remainder of the isolated product 'appears to be dimeric'. Pinnick and coworkers[197] confirmed these results.

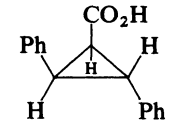
A different result was obtained later by Warner and Le[198] who showed that when the reactions were performed at room temperature it was possible to alkylate and to silylate **217**. It was also found that **217** remained unchanged after 22 h at 80°C. Thus only the reversible aldol formation appeared to be unfavorable in this instance. Jahngen[199]—coauthor with Krapcho[196]—recently confirmed the results of Warner and Le. In addition he found that the earlier formulated 'dimeric' product[196] was the condensation product 1-(cyclopropylcarbonyl)cyclopropanecarboxylic acid.

The problems with α-deprotonations of salts of carboxylic acids are also nicely exemplified by a study of Ford and Newcomb[200] with the isomeric acids **218** and **222**. Reaction of the *cis, trans* acid **218** with LDA in THF at 0°C for 30 min resulted in the desired allyl anion **220** which was protonated to give the two isomeric α-benzylcinnamates (**221**).

In contrast the *trans, trans* acid (**222**) was deprotonated at the *benzylic* position to give the allyl anion (**224**), which upon protonation gave as expected, **225**. It has not been possible to prove the existence of the cyclopropyl anions **219** and **223** (only in the case of the methyl ester enolates the cyclopropyl anion corresponding to **219** has been shown by deuteration to exist at − 78°C). Thus, deprotonation of cyclopropyl carbonyl compounds may be strongly dependent on the structural details of the cyclopropane, as previously demonstrated by the relative acidities of **209** and **210**.

Of interest, with regard to synthetic applications are *cyclopropane ester enolates* and their reactions.

Unsuccessful attempts to α-methylate the carboethoxy cyclopropane **226** have been reported by Fitzsimmons and Fraser-Reid[201].



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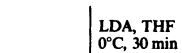

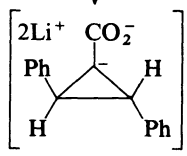

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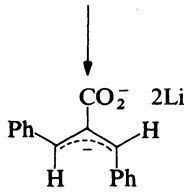

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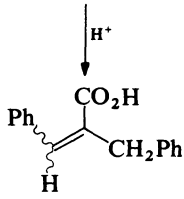

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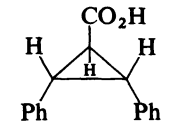

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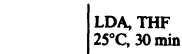

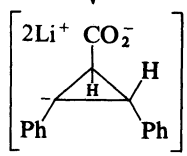

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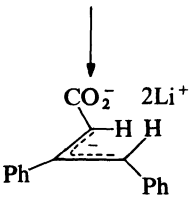

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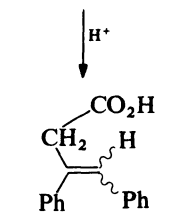

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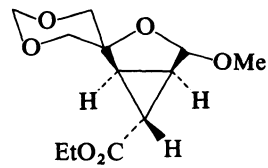
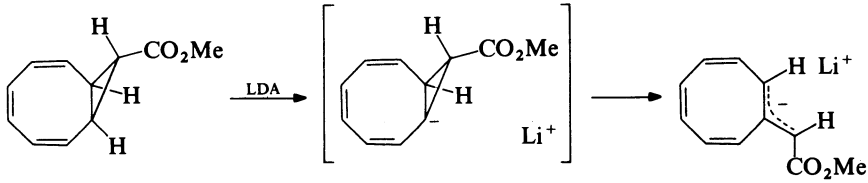
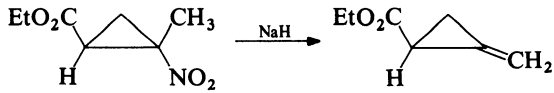


(226)

The low tendency of cyclopropyl esters to form the ester enolate is also documented by the following examples: Boche and Martens[202] have reported that methyl *cis*-bicyclo[6.1.0]nona-2,4,6-triene-*anti*-9-carboxylate (**227**) loses a proton at C(1) when treated with LDA to give, probably via the cyclopropyl anion **228**$^-$, the allyl anion **229**$^-$. Russell and coworkers[203] have shown that ethyl 2-methyl-2-nitrocyclopropanecarboxylate (**230**) gives the 2-methylenecyclopropanecarboxylate (**231**) when treated with sodium hydride.

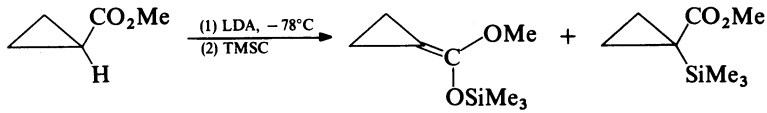


(227) (228$^-$) (229$^-$)



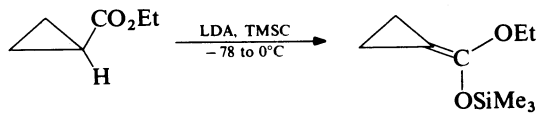
(230) (231)

A successful trapping reaction of a cyclopropyl ester enolate with trimethylsilyl chloride (TMSC) was first performed by Ainsworth and coworkers[204]. In the reaction of **232** with lithium diisopropyl amide at $-78°C$, followed by addition of TMSC, the ketene acetal **233** was formed in 10% yield as well as the silylated cyclopropane **234** (40%). Ketene acetals other than **233** are formed in yields > 90%.

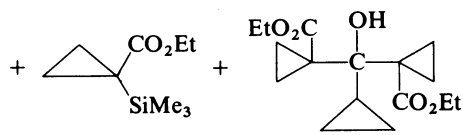


(232) (233) (234)

Pinnick and coworkers[197] reported similar attempts to α-functionalize ethyl cyclopropanecarboxylate (**235**) by treatment with base. Depending on the reaction conditions they were able to isolate the ketene acetal (**236**) and the α-silylated ester (**237**) as analogously reported by Ainsworth and coworkers[204].



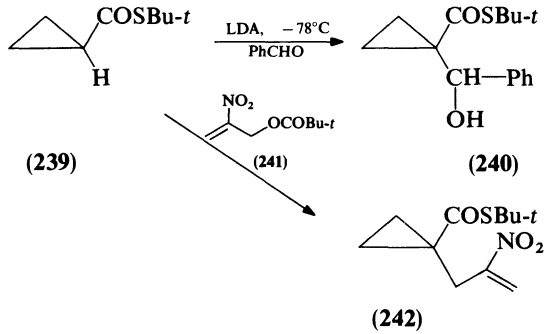
(235) (236)



(237) (238)

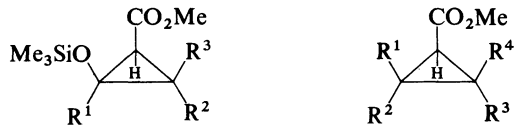
In addition, **238** was found which is undoubtedly the result of a two-step Claisen-aldol sequence. The formation of **238** has been confirmed by Seebach and coworkers[205a]. This clearly indicates that the anion of ethyl cyclopropanecarboxylate is formed by the action of LDA on **235**, but that the anion is very reactive in agreement with the low acidity of **235**. When trityllithium reacted with **235** only **238** was obtained after quenching with AcOD. Potassium hydride together with several trapping reagents gave neither **238** nor the expected trapping products.

Because of the difficulties encountered in the case of the esters **232** and **235** Wemple[206] investigated similar reactions with *thiol esters* of cyclopropanecarboxylic acids. As shown, deprotonation of **239** with LDA followed by treatment with benzaldehyde leads to **240** in 76% yield.



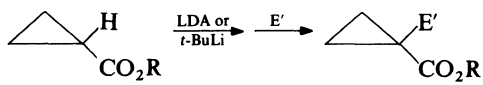
Knochel and Seebach[207] similarly converted **239** to **242** by condensation with **241**. The successful reaction of the thiol ester enolate anion of **239** with electrophiles seems to result from the higher kinetic acidity of the thiol ester as compared to the acidity of the normal ester[208].

Thorough investigations on the deprotonation and diastereoselective alkylation of 2-siloxy[209a] and other substituted methyl cyclopropanecarboxylates, **243** and **244**, respectively, have recently been published by Reissig[209b].



(243) **(244)**

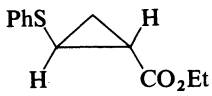
Most importantly with regard to the topic of this chapter, all cyclopropanecarboxylates may be deprotonated with LDA at −78°C (normally after 2 h). The question is whether it is possible to trap these energy-rich enolates with, for example, alkylating reagents, before self-condensation occurs with not yet deprotonated ester. Whether one is successful or not is a function of the substituents R^1–R^3 in **243** and R^1–R^4 in **244** as indicated early by the results of Kohler[186] and Smith and their coworkers[187] with, for example, **195** and **198**, and by the following data published by Koyanagi and coworkers[210]. Although additional substituents may increase the acidity of the hydrogen atom α to the carboxylate group, at the same time steric hindrance by these substituents can cause self-condensation to be unfavorable. Steric hindrance of self-condensation should also be responsible for the high-yield transformations of the esters **244a** and **b** with LDA or *t*-butyllithium followed by reaction with electrophiles E like alkyl halides, aldehydes or acid chlorides into **244-E'a** and **b**[205b]



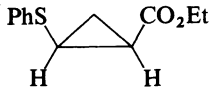
(244) **(244-E')**

a: R = *t*-butyl
b: R = 2,6-di-*t*-butyl-4-methylphenyl
For further synthetic preparations see Section IV.D.

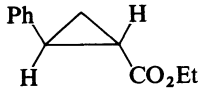
Koyanag and coworkers[210] have determined the relative acidities of the *cis/trans* isomeric phenylthiocyclopropanecarboxylates **245** and **246**, respectively, as compared to phenylcyclopropane carboxylate (**247**). H/D exchange experiments have shown that the ester **245** is 18.4 and **246** is 8.0 times more acidic than **247**. Thus, a *cis*-phenylthio group stabilizes a negative charge much better than, for example, a phenyl group.



(245)



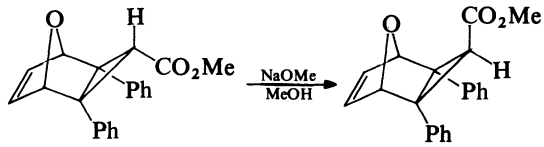
(246)



(247)

One could envision a stabilization of the gegenion by the sulfur atom as the underlying reason. Again, no *cis* ⇌ *trans* isomerization takes place during the H/D exchange reaction (ethanol, pyridine, 70° C). Unfortunately, no quantitative data are available as to the acidity of cyclopropanes like **195** and **198** which are 'heavily loaded' with acceptor substituents.

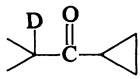
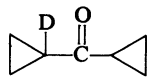
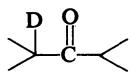
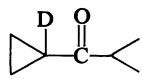
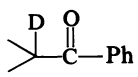
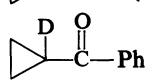
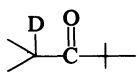
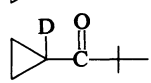
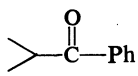
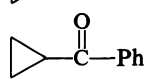
Base-catalyzed stereoisomerization of the cyclopropyl carboxylate **248** to give **249** has been observed by Martin and coworkers[211].



(248) **(249)**

De Boer[190, 191] and Rappe[212] and their coworkers were the first to report on quantitative measurements of the kinetic acidity of cyclopropyl C(O)R-substituted compounds in comparison to their open ring analogs, the corresponding isopropyl species. Bordwell and

TABLE 25. Relative rate constants for the exchange reaction of RD in MeONa/MeOH at 53.2°C[190, 191]

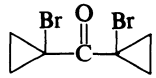
Isopropyl	$k_{D,rel}$	Cyclopropyl	$k_{D,rel}$	$\frac{k_{iso}}{k_{cyclo}}$
	1330 ± 100		1	1330 ± 100
	1550 ± 100		1.8 ± 0.2	850 ± 100
	4000 ± 400		24 ± 2	170 ± 20
	4.4 ± 0.3		0.42 ± 0·65	10 ± 2
	24.7		28.2	

[a] Equilibrium acidities (pK_a) in DMSO.

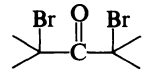
coworkers have measured equilibrium acidities in dimethyl sulfoxide[213]. Their data are presented in Table 25.

The data from Table 25 clearly emphasize the lower acidity of *cyclopropyl ketones* as compared to *isopropyl ketones*, the factor ranging from 1330 to 10 in the case of the *t*-butyl species. These data are in contrast to earlier findings of Shechter and coworkers who reported that an α-hydrogen atom in benzoylcyclopropane exchanges 14 times faster than in isobutyrophenone, but they agree with later work of this group[214]. Breslow[215] compared the relative rates of cyclopropyl and cyclopropenyl ketones with regard to antiaromaticity of the cyclopropenyl anion. This is expected for a largely *mesomeric* substituent leading to a planar enolate anion which adds additional strain, as pointed out in earlier publications[188,214c,216a].

The instability and high reactivity of cyclopropyl enolates encountered throughout in this chapter are also nicely documented by electrochemical reductions of bis(α-bromocyclopropyl)ketones[217]. Reduction of cyclopropane **250** requires a much more negative potential than, for example, reduction of the ring-opened reference substance **251**.



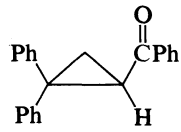
(250)



(251)

$E_{1/2}$ V(vs. S(E)) −0.85 −0.23

That it is indeed the planarity of cyclopropyl (ester) enolates that causes extra strain and thus instability and high reactivity of such anions, as well as low acidity of the corresponding C(O)-substituted cyclopropanes, has been firmly established[191c,216g]. It was shown that treatment of (−)-(*R*)-1-benzoyl-2,2-diphenylcyclopropane ((−)-(*R*)-**252**) with 0.1 M sodium methoxide in methanol-O-D gave $k_{rac}/k_{ex} = 1$; this means that the anion is planar.

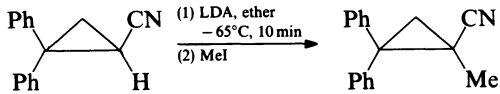


((−)-(*R*)-**252**)

b. α-Cyano

Pioneering work with cyclopropyl nitriles, their acidities, stereochemistry and the reactions of the corresponding carbanions has been published by Walborsky and coworkers[216b-f].

Optically active (−)-(*R*)-**253** is deprotonated by LDA in ether at −65°C completely in less than 10 min, as shown by methylation, to give the racemic product **254**.

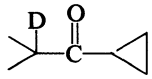
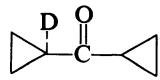
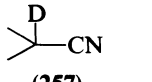
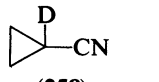
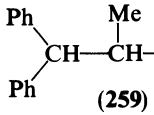


((−)-(*R*)-**253**) racemic (**254**)

When H/D exchange was performed with 1.0 M sodium methoxide in methanol-O-D the ratio of racemization (k_{rac}) to exchange (k_{ex}) was 1.2×10^{-4} corresponding to 99.9% retention of configuration. This is evidence for a *pyramidal* anion which has a considerable barrier to inversion.

Comparison of cyclopropyl nitriles with isopropyl nitriles, and of the nitriles with the corresponding ketones is accessible from work of Walborsky[216], and de Boer[190,191] and their coworkers (Table 26).

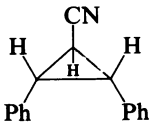
TABLE 26. Relative rate constants k_D for H/D exchange reactions

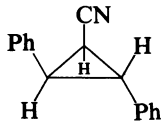
Isopropyl	$k_{D,rel}$	Cyclopropyl	$k_{D,rel}$	$\frac{k_{iso}}{k_{cyclo}}$
 (255)	1330 ± 100^a	 (256)	1^a	1330 ± 100
 (257)	0.81 ± 0.06^a	 (258)	11.8 ± 0.7^a	0.067 ± 0.006
 (259)	$1^{b,c}$	((−)-(*R*)-**253**)	$31^{b,c}$	0.033

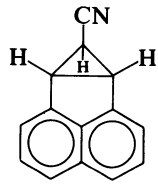
[a] MeONa/MeOH at 53.2°C[191].
[b] MeONa/MeOD at 50.0°C[216].
[c] The relative rates of (−)-(*R*)-**253** and **259** are not related to the data of **255–258**.

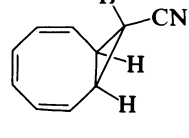
A comparison of compounds (−)-(*R*)-**253** and **255–259** clearly demonstrates that the cyclopropyl nitriles (−)-(*R*)-**253** and **258** are more acidic than their open-ring analogs **259** and **257**, respectively. This situation is reversed to what is observed in the ketone series **255** and **256**. Thus, deprotonation α to a cyano group does not lead to a compound which is similarly strained as cyclopropyl enolates, or (in agreement with the ratio $k_{orac}/k_{ex} = 1.2 \times 10^{-4}$ observed with (−)-(*R*)-**253**), a cyano group stabilizes a negative charge at a *pyramidal* C-atom much better than a C(O)R-group. Thus, in the case of the C(O)R group mesomeric stabilization is more important than in the case of the cyano group which stabilizes largely via its dipole (field) effect as well. A recent X-ray structure determination of α-cyano-benzyllithium is in agreement with this conclusion[218b].

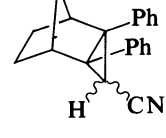
The literature offers more examples of facile deprotonations of cyclopropyl nitriles. Boche and coworkers[202,218a,219] and Ford and Newcomb[200b,c] observed the deprotonation of the nitriles **260** and **261** as well as their alkylation; **262** has been deprotonated by Wittig and coworkers[90a]. Similarly, **263** is easily deprotonated to give the α-cyano anion—in contrast to the corresponding ester **227** which is deprotonated exclusively at C(1) instead[202]! Compound **264** also gives the corresponding α-cyano cyclopropyl anion[164].


(260)


(261)


(262)


(263)

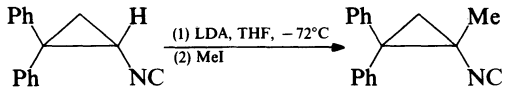

(264)

Pinnick and coworkers[197] reported that addition of cyclopropanecarbonitrile to LDA in THF at −78°C (LDA and similar bases have also been used in the reactions of **260–264**)

followed by allyl bromide gave after warming to room temperature the expected allyl nitrile. Deprotonation with potassium hydride and reaction with allyl bromide, benzaldehyde and methyl benzoate, respectively, failed however to give any of the expected trapping products. This, of course, may be due to the potassium hydride reacting with the nitrile group itself.

c. α-Isocyano

It has been demonstrated by Walborsky and Periasamy[220,221] that, in contrast to the 1-cyano-2,2-diphenylcyclopropyl anion (see above), the 1-isocyano-2,2-diphenylcyclopropyl anion in ether solvents is configurationally stable at −72 °C: deprotonation of (+)-(*S*)-**265**

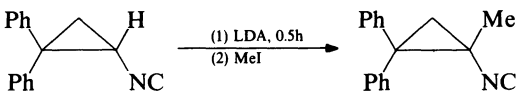


((+)-(*S*)-**265**) ((+)-(*S*)-**266**)

with LDA in THF at −72 °C, followed by reaction with methyl iodide led to (+)-(*S*)-**266** with almost complete retention of configuration (99% o.p.).

The barrier to the inversion imposed by the isocyano group permitted the evaluation of the effect of gegenion, solvent and temperature on this cyclopropyl anion. As is evident from Table 27 only at −5 °C is the loss of configuration very rapid. This would be consistent with the view that there is a great deal of ionic character associated with the lithium–carbon bond[221].

TABLE 27. Effect of temperature on configurational stability



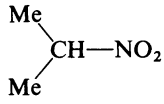
Temp. (°C)	((+)-(*S*)-**265**) Yield (%)	((+)-(*S*)-**266**) Optical purity (%)
−72±2	96	98
−52±1	75	93
−25±1	92	58
−5±1	80	0.3

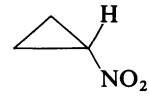
Moreover, using the cation exchange technique[222] the lithium cation was exchanged for sodium and potassium cations and the stereochemical results were the same as for lithium: essentially complete retention of configuration at −72 °C. Finally, at −72 °C changing the solvent to a mixture of THF and dimethoxyethane or adding cation complexing reagents such as TMEDA, triglyme or HMPA also resulted in complete retention of configuration. Even the addition of crown ethers such as 12-crown-4, 15-crown-5, 18-crown-6 or dicyclohexyl-18-crown-6, did not affect the configurational stability of the 1-lithio-1-isocyano-2,2-diphenylcyclopropane.

Hence, in the case of the electronegative isocyano group which possesses a π-system for delocalization (as the carbonyl and the nitrile group) but additionally a non-bonding pair of electrons on nitrogen, even a 'free' or 'naked'[223] anion is capable of maintaining its configuration.

d. α-Nitro.

Nitrocyclopropane is about 10 orders of magnitude less acidic than its open chain analog 2-nitropropane[191c, 213, 214c] as determined in DMSO (equilibrium acidities)[213].

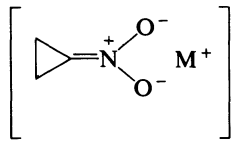




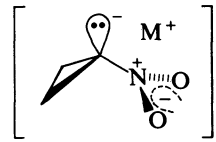
p*k*(DMSO) 16.89 ±0.02 ~ 27

Bordwell and coworkers[213] note that nitrocyclopropane under the conditions of exchange rapidly decomposes. Thus, the nitrocyclopropyl anion is not easily formed and is therefore very reactive, similar, for example, to cyclopropyl ethyl ester enolates (Section IV.B.1.a).

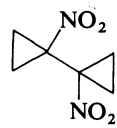
The p*K* measurements are nicely supported by efforts of Seebach and coworkers to get hold of the 'elusive' nitrocyclopropyl anion[205a]. When nitrocyclopropane was treated at temperatures between −80 and −110° C with bases such as butyllithium, LDA or potassium hexamethyldisilylamide in THF, yellow to red solutions have been obtained which were thought to contain the lithium salt of acinitrocyclopropane (**267a**). Workup after any amount of time, raising the temperature, or addition of any electrophile with or without oxidizing properties, always led to the isolation of mixtures of the colorless dinitro-compound **268**, and of the deep-blue nitro-nitroso compound **269**.



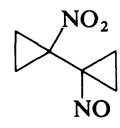
(**267a**)



(**267b**)



(**268**)

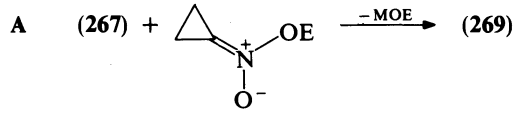


(**269**)

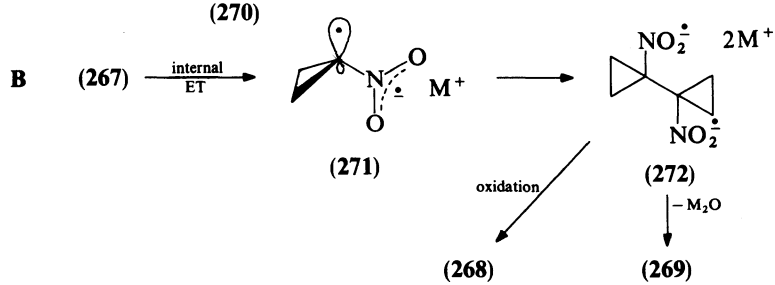
The nitronate **267** 'might be expected not to have a planar structure **267a** but to be the bent species **267b**, stabilized more by polar than conjugative effects'[205a].

The formation of **268** and **269** is believed to occur by two possible pathways[205a]:

(1) reaction of the probably very reactive nitronate **267** with the probably very reactive products **270** resulting from **267** by addition of an electrophile E^+ to an oxygen atom (route **A**). This is followed by loss of MOE to give **269**. This route is similar to the one leading to the self-condensation product **238** formed from the cyclopropane carboxylate **235** with LDA.



(**270**)



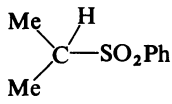
(2) An ET-mechanism would be also in accord with the results (route **B**). Internal ET within **267** should give the cyclopropyl radical–nitro radical anion species **271** which might easily dimerize to give **272**. On addition of electrophiles/oxidants the observed products **268** and **269** would be formed.

The question whether the nitrocyclopropyl anion might have a triplet structure (possibly similar to **271**) is discussed in Section IV.B.1.l.

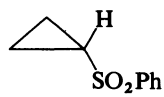
The solid state structure of [α-nitrobutyllithium ethanol]$_n$ has recently been determined[242b].

e. α-Sulfonyl and derivatives

As far as the situation of the sulfonyl group and derivatives of the sulfonyl group is concerned, there are conflicting results in the literature—at least at first sight. Zimmerman and Thyagarajan[224] (measurements in ether and hydrocarbon solvents) and Cram and coworkers[225] (measurements in DMSO) reported that the equilibrium acidities of isopropyl- and cyclopropyl phenyl sulfone, **273** and **274**, respectively, are roughly equal.



(273)



(274)

De Boer and coworkers' H/D exchange measurements[190,191] ($k_{H,rel}$ for the exchange of 30% of RH in MeOD/MeONa (0.22 M) at 53.2°C) indicate a lower acidity of the open-chain **273** than of the cyclopropane derivative **274** ($k_{273}/k_{274} = 0.029 \pm 0.001$).

Bordwell and coworkers[213], on the other hand, report the following equilibrium acidities in DMSO (Table 28).

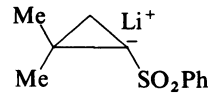
TABLE 28. Cyclopropyl effects on equilibrium acidities in DMSO[213]

X	pK_a(Me X)	pK_a 	ΔpK
S(O)($\overset{+}{N}$Me$_2$)Ph	14.4	20.9 ± 0.3	6.5 + 0.3
SO_2CF_3	18.8	26.6	7.8
S(O)(NSO$_2$Ph)Ph	24.5	28.8 ± 0.2	4.3 ± 0.2
SO_2Ph	29.0	> 32	> 3.0

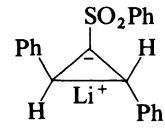
According to these results the sulfone and the related sulfoximine and oxosulfonium cation groups lead to higher acidities of the methyl derivatives. The corresponding cyclopropanes are less acidic. Isopropyl phenyl sulfone (**273**) has a pK value > 32 (the pK_a limit in DMSO), as does cyclopropyl phenyl sulfone (**274**)[213] (which, of course, does not exclude equal acidities). From his results, Bordwell[213] reaches the conclusion that the similarity of cyclopropyl effects on acidities in substituted cyclopropanes when the substituent is NO_2, C(O)R, SO_2CF_3, S(O)(N^+Me_2)Ph or S(O)(NSO$_2$Ph)Ph can be interpreted in terms of a demand for p character from cyclopropyl anions, which suggests that α-sulfonyl carbanions, as well as nitronate and enolate anions, have planar structures. The α-C atom in [α-(phenylsulfonyl)-benzyllithium-tetramethylethylenediamine]$_2$ has recently been shown by Boche and coworkers to be planar in the solid state[226a]. This result was confirmed by a study of Gais and coworkers[226b] on the structure of [CH_2(SO$_2$Ph)Li(TMEDA)]$_2$. As far as the structure of a cyclopropyl α-sulfonyl anion is concerned, Zimmerman and Thyagarajan[224] conclude from their data that only some of the stabilization derives from electron delocalization and that there is only an approach to

the planar geometry associated with such stabilization. Cram and coworkers[225] similarly favor a pyramidal structure in the cyclopropyl case.

At the moment the question—planar or pyramidal cyclopropyl α-sulfonyl anion—is not settled. There seem to be, however, more arguments in favor of a pyramidal structure. Cram[225] performed NMR measurement with the lithium species **275** in DMSO/THF between 30 and 80°C which indicates definitively that this anion is very 'stable'. The NMR measurements do not, however, allow one to distinguish between an inversion of the pyramidal species **275** and a hindered rotation around the C–S bond of a planar anion.

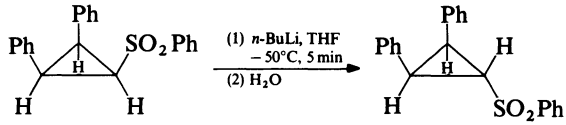


(275)



(276)

The lithium salt **276** has been prepared by Boche and coworkers[219] with MeLi in ether, *n*-BuLi in THF and LDA in THF; it reacts with D_2O to give the corresponding 1-D-compound. Thus, **276** is also comparatively 'stable'. The *cis,cis*-sulfone **277** reacts with *n*-BuLi in THF, followed by protonation after 5 min, to give the *trans,trans*-sulfone **278** (undoubtedly via the corresponding Li compounds at which stage the isomerization takes place although stereoselective protonation of a pyramidal *or* planar carbanion is not excluded)[215a, 219].

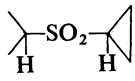


(277) **(278)**

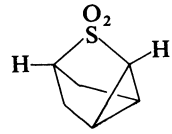
It thus seems that there is no problem to prepare cyclopropyl α-sulfonyl carbanions—like the α-cyano species which have been shown experimentally to be pyramidal[216]. This is in striking contrast to the situation of the α-NO_2 and α-C(O)R-cyclopropyl anions which are difficult to prepare, extremely reactive and, at least in the case of the enolates, planar.

As far as the previously mentioned 'conflicting' p*K* results are concerned it is important to note that Zimmerman's and Cram's *equilibrium* acidities have been determined in ether, hydrocarbon solvents and in DMSO, respectively. This excludes a solvent effect at least in these solvents, as being responsible for the almost equal acidities of **273** and **274**. The situation, however, may be different in the case of de Boer's *kinetic* acidity measurements in methanol resulting in a higher acidity of the cyclopropyl sulfone **274**. Bordwell's higher acidity of the *methyl* sulfone also does not exclude **274** have the same acidities: one should use the less acidic isopropyl and not the methyl sulfones in a comparison with the cyclopropyl sulfones. Very recent H/D exchange measurements (0.5 NaOD/D_2O) by Kirmse[279] support the suggestion that the pyramidal configuration of the anionic C atom of an α-sulfonyl carbanion is not necessarily unfavorable. Thus, the cyclopropyl α-hydrogen in **278a** is kinetically more acidic ($k[s^{-1}]$, 75°C) than the isopropyl hydrogen. This is also the case in the tricyclic sulfone **278b** ($k[s^{-1}]$, 35°C) in which planar configurations of the anionic C atoms are hard to imagine. The comparatively high acidity of **278b** is also remarkable.

Interesting results as far as a possible pyramidal configuration of an α-sulfonyl cyclopropyl anion is concerned are furthermore supplied by the results in the following section and in Section I.



(278a)

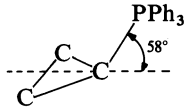


(278b)

75°C $1.2 \cdot 10^{-6}$ $2.6 \cdot 10^{-4}$ $1.1 \cdot 10^{-6}$ $1.5 \cdot 10^{-3}$
35°C $4.3 \cdot 10^{-6}$

f. α-Triphenylphosphonium and α-phosphonyl

Triphenylphosphonium cyclopropylide (**279**), although not a 'carbanion', is of interest because its structure has been determined by X-ray crystallography by Schmidbaur and coworkers[227]. The most important feature is the pyramidal configuration of the ylidic C-atom: the P-atom is bent out of the plane of the cyclopropyl carbon atoms by 58°! There is no analogy to planar methylenecyclopropanes like **280** nor to other ylids all of which are planar[227a]. As Schmidbaur points out[227a] the description of the ylid 'double bond' is becoming a problem.



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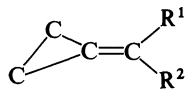
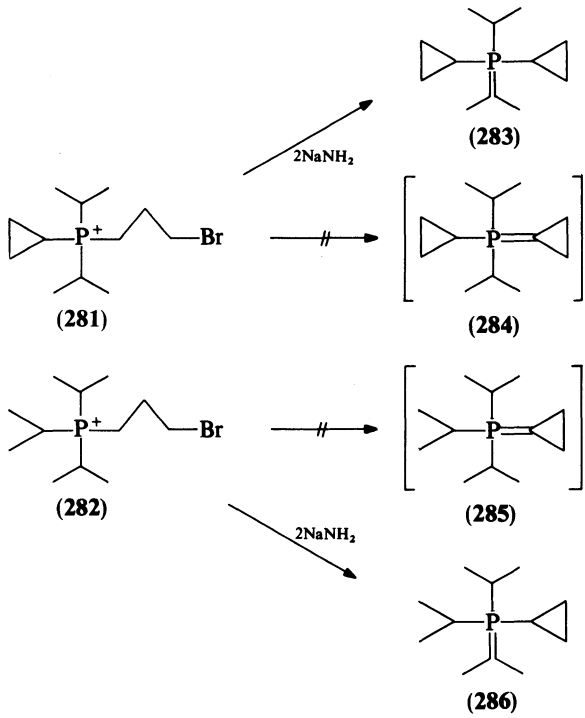


(280)

This is even more so if one compares the relative acidities of the hydrogen atoms in the isopropyl and cyclopropyl substituents of the phosphonium salts **281** and **282**.



(281) (283) (284) (282) (285) (286)

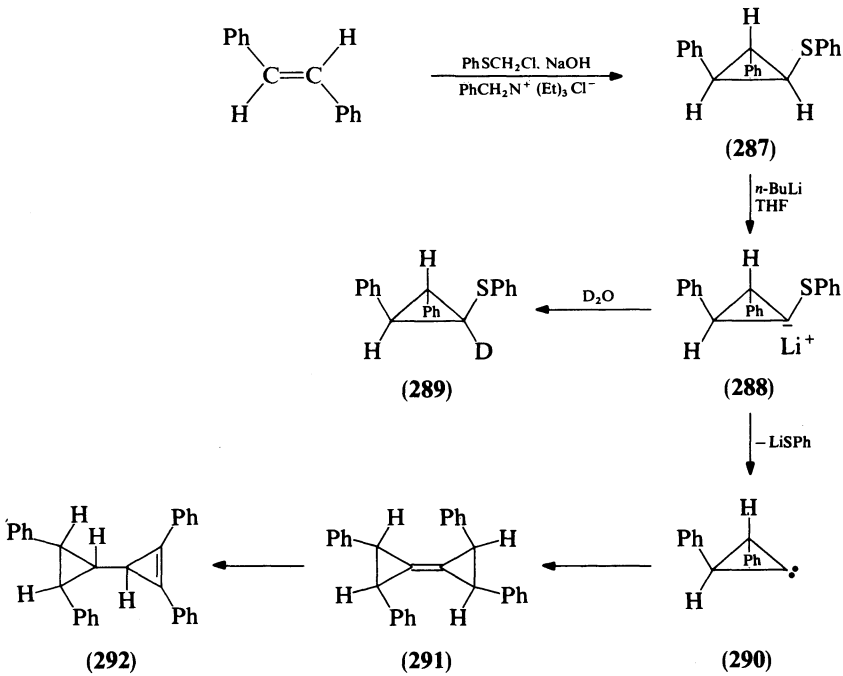
Deprotonation of **281** (**282**) does not give the cyclopropylid **284** (**285**); rather the isopropyl group is deprotonated to give **283** (**286**)[227b]. It is concluded from the low acidity of the cyclopropyl hydrogens in **281** and **282** that the carbanion-stabilizing properties of the phosphonium substituent are not only inductive in nature but that delocalization of the negative charge should also be important[227b].

The X-ray structure of the pyramidal and thermally very stable ylid **279**, however, rigorously excludes that the cyclopropyl hydrogens of the phosphonium salts **281** and **282** might be less acidic than the isopropyl hydrogens because in the latter the ylid is planar, as is the case with cyclopropyl enolates! Does R_4P^+ really lead to a 'violation of the acidity rule'[227b]?

It may rather be that in the case of third row substituents like R_4P^+ the relative acidity of cyclopropyl and isopropyl hydrogens is not as indicative of the carbanion configuration as in the case with the second row substituents C(O)R, CN and possibly NO_2. As far as cyclopropyl sulfones are concerned one would therefore predict that the corresponding α-sulfonyl cyclopropyl anions may have a pyramidal configuration. The deprotonation of cyclopropyl phosphonates, followed by reaction with aldehydes, was recently published by Hirao and coworkers[227d,e].

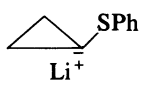
g. α-Sulfide, α-sulfoxide and α-diphenylsulfonium

The facile preparation of cyclopropane sulfides, e.g. **287**, by means of a phase transfer catalyzed reaction has been described by Boche and Schneider[228].

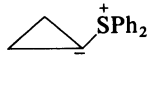


The lithium species (**288**) is easily accessible by deprotonation with *n*-butyllithium in THF, as shown by deuteration to give **289**[219]. The concomitant formation of **292** is probably due to the carbenoid nature of **288**. Dimerization of the cyclopropylidene **290** should give **291** which under basic conditions isomerizes to give **292**[219].

The configurational stability of such anions has been demonstrated by Trost and coworkers[229].



(293)



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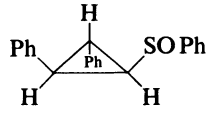


(295)

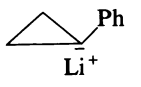
It has been found that the AA'BB' type NMR spectrum of **293** shows no temperature dependence between $-78°C$ and ambient temperature. The higher barrier to inversion compared to the α-sulfonyl anion **275** may be attributed to lone pair–lone pair repulsions that destabilize the flattening of the carbon atom, an effect similar to that found for the anion of the isocyanide **265**[221] (see above).

The inversion in the case of the diphenylsulfonium ylide **294** is also slow on the NMR time scale[229].

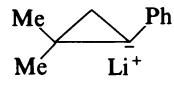
The anion of the cyclopropyl sulfoxide **295** has been prepared with *n*-butyllithium in THF at $-20°C$[219] as shown by deuteration. The stereochemistry of the anion has not been investigated so far.

h. α-Phenyl, α-vinyl and α-acetylene

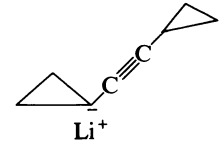
1-Lithio-1-phenylcyclopropane **296** has first been prepared by Schlosser[230]; the pyramidal structure and dynamic behaviour of **297** have been investigated by Müllen and coworkers[231] who showed that it isomerizes at 4°C with a free energy of activation $\Delta G^{\ddagger}_{(4°C)} = 13.4 \pm 0.5$ kcal mol^{-1}.



(296)



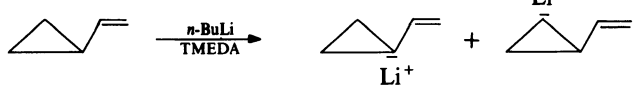
(297)



(298)

A similar situation is observed in cyclopropyl(1-lithiocyclopropyl)acetylene (**298**). The compound has a pyramidal configuration at the anionic carbon atom but isomerization occurs easily at a rate which is dependent on the composition of the benzene/THF mixture[232]. In the case of **297** the phenyl substituent should stabilize the negative charge mostly by delocalization while the acetylenic group in **298** should operate more inductively.

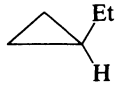
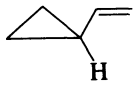
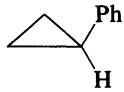
The reaction of vinylcyclopropanes[233] with *n*-butyllithium/TMEDA leads to several lithium species: **299**, for example, gives mainly **300**, but also **301**.



(299) (300) 50% (301) 20%

Thus, there is not much preference for the formation even of the 'allyl' species **300**, possibly because it has a pyramidal configuration at the carbanionic C-atom.

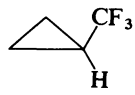
Shatenstein and coworkers performed kinetic acidity measurements[234] with **302**, **299** and **303** by exchange with KND_2/ND_3 and obtained the following rate constants.

	Temp. (°C)	k (s^{-1})
 **(302)**	120	$\sim 10^{-7}$
 **(299)**	25	$\sim 10^{-4}$
 **(303)**	25	$\sim 10^{-4}$

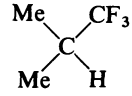
The ethyl-substituted **302** does not exchange at 25°C; only at 120°C is exchange observable; however, at much slower rate than with **299** and **303** whose acidities are comparable.

i. α-Trifluoromethyl

The kinetic acidity of trifluoromethyl cyclopropane (**304**) and of the corresponding isopropyl compound **305** have been determined by de Boer and coworkers[190,191]. As expected for the inductively operating CF_3 group the cyclopropyl compound **304** exchanges with deuterium $5 \times 10^3 - 5 \times 10^4$ times faster than **305**.



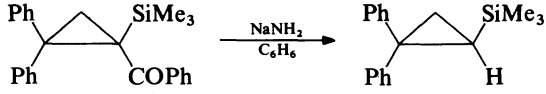
(304)



(305)

j. α-Trimethylsilyl, methyl, chloro, fluoro and methoxyl

It has been shown recently by Paquette and coworkers[235] based on the earlier work of Walborsky and coworkers[236] that under the conditions of a Haller–Bauer cleavage the optically active ketone **306** is transformed into the optically active trimethylsilyl species **307** with complete retention of configuration.



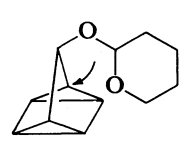
((+)-(*R*)-**306**) ((−)-(*R*)-**307**)

Thus, under the reaction conditions the intermediate α-trimethylsilyl anion is configurationally stable. One should also mention that the Haller–Bauer cleavage proceeds with complete retention of configuration when Me[236], H[237] and possibly Cl[236], F[236] and OMe[236] replace the $SiMe_3$ of **306**.

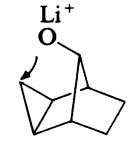
k. β-Alkoxyl

Ortho-lithiation of aromatic compounds has become a useful synthetic reaction[238]. It is interesting that similar methodology also provides selectivity in the lithiation of cyclopropanes. Klumpp and coworkers reported[239] on the directed lithiation of cyclopropylcarbinyl ethers, as shown by the arrow in the following examples.

BuLi, hexane
64 h, 56%

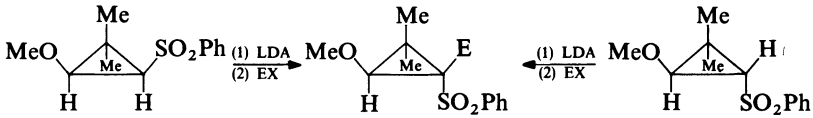


BuLi, hexane
20 h, 80%



i-prop. Li, ether/pentane
48 h, 76%

Padwa and Wannamaker[239c] have also demonstrated the remarkable effect of a β-methoxy groups. The carbanion obtained by deprotonation of either *cis*- or *trans*-2,2-dimethyl-3-methoxycyclopropyl phenyl sulfone with LDA at −78°C reacted smoothly with a variety of electrophiles EX(D_2O, MeI, CH_2CHCH_2Br, $ClCO_2Me$) to give exclusively a single stereoisomer in which the electrophile was *cis* to the methoxy group.



l. α-Substituent effects: theoretical studies

In order to examine whether the acidities observed in α-C(O)R, α-NO_2, α-CN and α-CF_3 substituted cyclopropanes are correctly explained by a predominating mesomeric effect in the case of the α-C(O)R and α-NO_2 substituents, and a stronger dipole (field) effect with α-CN and α-CF_3 substituents Wagner and Boche[240] investigated this subject by means of STO-3G calculations. It was of interest to determine whether the calculations are able to reproduce the relative acidities of cyclopropyl and isopropyl compounds, as well as the configuration of the corresponding cyclopropyl anions.

Table 29, column 1 reveals the influence of a substituent X in comparison to H at a methyl group. Columns 2 and 3 give the relative acidities of X-substituted 2-propanes and cyclopropanes. As one can see, the mostly mesomerically stabilizing substituents CHO,

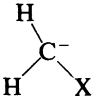
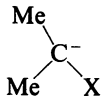
TABLE 29. Calculated proton affinities (kcal mol^{-1}) related to the calculated proton affinity of CH_3^- (= 559.7 kcal mol^{-1})[240]

X			
H	0	−15.8	−32.0
CF_3	−44.9	−45.1	−61.6
CN	−63.0	−69.0	−75.4
CHO	−56.8	−66.3	−60.6
COOH	−62.8	−69.7	−64.7
NO_2	−84.5	−93.1	−88.2

COOH and NO_2 acidify the 2-propanes more than the cyclopropanes, thus confirming that they create I-strain to delocalize the negative charge of the cyclopropyl anion in those cases. The opposite applies for CN and CF_3. Both results are in excellent agreement with the experimental results discussed in earlier sections.

Next, the energy difference between the planar and the pyramidal configuration has been calculated (Table 30).

TABLE 30. Energy difference (kcal mol^{-1}) between planar and pyramidal carbon configuration[a]

X			
H	23.9	18.4	32.5
CF_3	10.5	2.1	22.4
CN	0.5	0	9.3
CHO	0	0	0.7
COOH	0	0	1.9
NO_2	0	0	11.9

[a] Zero means that the planar structure is an energy minimum[240].

In agreement with Walborsky's results[216] and a recent X-ray structure determination of α-cyano-benzyllithium[218b] the calculations nicely show that $H_2\bar{C}$–CN (0.5 kcal mol^{-1})[241] and $Me_2\bar{C}CN$ (0 kcal mol^{-1}) have almost no inversion barrier while the α-cyano cyclopropyl anion has a sizeable one (9.3 kcal mol^{-1}). Whether in the case of the CHO and COOH substituted cyclopropyl anions a pyramidal configuration with a very small barrier (0.7 and 1.9 kcal mol^{-1}, respectively) exists, is not clear. The barrier may be an artifact of the small basis set, and the enolates may well be planar. In any case, the calculations are again in agreement with the experimental result according to which k_{ex}/k_{rac} in the case of the optically active cyclopropyl phenyl ketone (−)-(*R*)-**252** is unity[216f] (see Section IV.B.1.a).

The NO_2 result is interesting: the anion is pyramidal according to the calculations and has a rather high barrier to inversion (11.9 kcal mol^{-1}). This indicates that the NO_2 group exerts not only a strong mesomeric effect (compare the acidities of the isopropyl and cyclopropyl NO_2 compounds in Table 29) but also a strong dipole (field) effect, which is supported by experimental facts[205a]. Other calculations of Wagner and Boche[242a] revealed a triplet ground state for the nitrocyclopropyl anion. This result would nicely explain the experimental findings with regard to the 'elusive' α-nitrocyclopropyl anion[205a] because it would quickly dimerize.

As far as the phenylsulfonyl substituent is concerned it has been demonstrated by means of recent 3-21G* calculations by Bors and Streitwieser[243] that in the methylsulfonyl-methyl anion **308** the dominating mechanism of carbanion stabilization can be described as a classical polarization involving the SO_2 group and n–σ^* orbital interactions. The carbanionic center is planar although d–p–π conjugation is not an important factor in stabilizing the anion.

$^-CH_2$–SO_2–Me (**308**) LiCH$_2$–SO_2–Me (**309**)

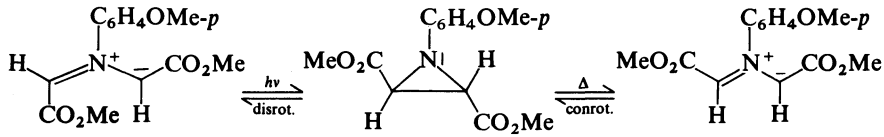
In the more realistic lithiomethyl methyl sulfone (**309**) the lack of importance of conjugative bonding is nicely demonstrated by the pyramidal carbanion center. This result

is important with respect to the relative acidities of 2-propyl and cyclopropyl sulfonyl compounds (Table 28, Section IV.B.1.e) and the structure of α-sulfonyl anions. It questions whether the 'low' acidities of the cyclopropyl compounds really mean that they are *planar*[213]. The formation of a pyramidal C-atom even in the case of **309** rather suggests a pyramidal structure of an α-sulfonyl cyclopropyl anion (see also the discussion in Section IV.B.1.f. in connection with the pyramidal structure of the cyclopropyl phosphonium ylid **279**).

C. Cyclopropyl–Allyl Anion Transformations

Although reactions of cyclopropanes as **195** or **198** with base to give ring-opened products have been investigated broadly by the groups of Kohler and coworkers[186] at the turn of the century and later by Smith and coworkers it has not been clearly established whether a cyclopropyl anion like **196** is formed as a discrete intermediate[187], or whether deprotonation and ring-opening to give the allyl anion **197** occur synchronously[188] (see page 768).

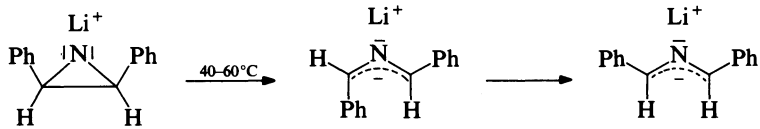
It was only after Woodward and Hoffmann in 1965 had predicted a conrotatory mode for the thermal cyclopropyl–allyl anion transformation[79] that a new interest developed in this reaction. By means of the iso-π-electronic aziridine **310** Huisgen and coworkers[244] succeeded in demonstrating that the thermal recation gave a conrotatory formation of azomethine ylid (**311**) and that the light-induced reaction resulted in a disrotation to give **312**.



(312) (310) (311)

The same stereochemical modes have been observed by the same group in the oxirane ⇌carbonyl oxide transformations[245, 246].

Kauffmann and coworkers[247] prepared *N*-lithio-*cis*-2,3-diphenylaziridine (**313**) which transforms into *endo,exo*-1,3-diphenyl-2-azallyllithium (**314**) at 40–60°C, this establishing the thermal conrotation in this system.

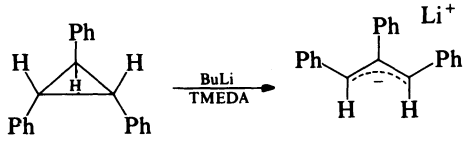


(313) (314) (315)

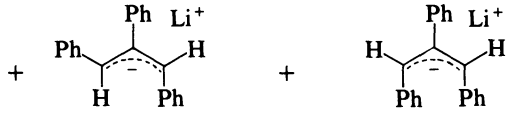
The isomerization of **314** to give **315** competes successfully with the trapping reaction of **314** with *trans*-stilbene which established the stereochemistry of **314**.

The cyclopropyl–allyl anion case itself turned out to be more of a problem. Mulvaney and Savage[248] reacted the *trans,trans*-1,2,3-triphenylcyclopropane (**316**) with *n*-butyllithium/TMEDA which led to one (or more) of the isomeric 1,2,3-triphenylallyl anions (**317**).

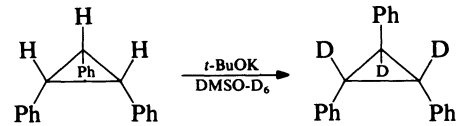
Since the corresponding *cis,cis*-isomer **318** with potassium *t*-butoxide in DMSO-d_6 led to the tris-deuterated *trans,trans*-cyclopropane **316**-D_3 Mulvaney and Savage concluded that the 1,2,3-triphenylcyclopropyl anion is capable of existing for a finite period of time as an intermediate without undergoing ring-opening. Therefore this cyclopropyl anion



(316)

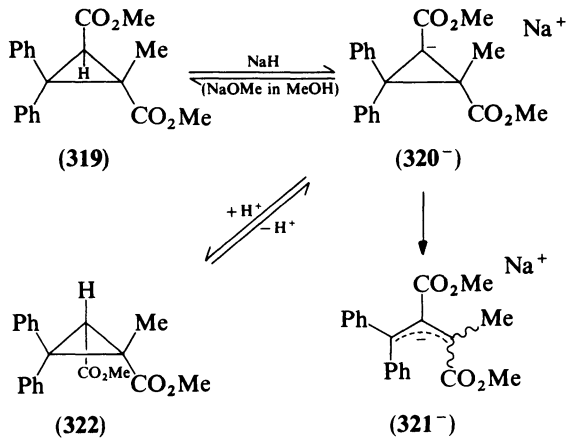


(317)



(318) (316–D_3)

should also be an intermediate in the reaction of **316** with *n*-butyllithium/TMEDA to give the allyl anion(s) **317**. Huisgen and Eberhard[249] arrived at similar conclusions with the cyclopropane **319**.



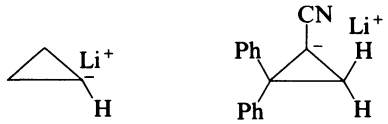
(319) (320$^-$)

(322) (321$^-$)

The cyclopropyl anion **320**$^-$ should be the intermediate both in the *cis–trans* isomerization to give **322** (NaOMe in MeOH) and in the ring-opening reaction (NaH in DMF) to give **321**$^-$ whose stereochemistry is unknown. From these studies it seemed reasonable that cyclopropyl anions did indeed thermally isomerize to give allyl anions.

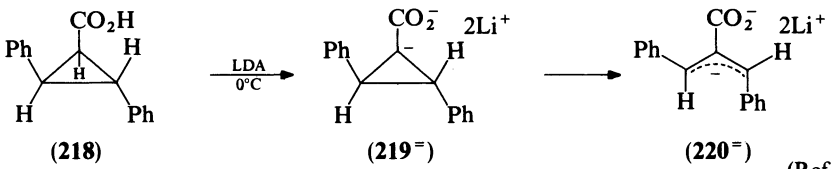
If one compares the 1,2,3-triphenylcyclopropyl anion as well as the cyclopropyl anion **320**$^-$ with the many more cyclopropyl anions not showing the ring-opening reaction such as all cyclopropyl 'anions' with H or alkyl groups at C(1) like the parent **323**[250] or Walborsky's **324**$^-$ [216] it is immediately clear that substituents which stabilize a negative charge at *both* carbon atoms which become terminal centers of the allyl anion facilitate the ring scission. If the cyclopropyl anion is prepared by deprotonation of a cyclopropane it is

additionally necessary to put the appropriate substituent at the forthcoming carbanionic carbon atom in order to provide regioselective deprotonation.

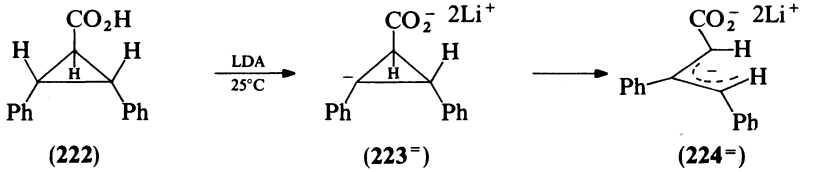


(323) (324)

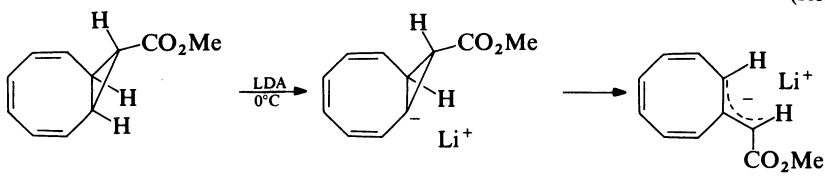
The necessity of both prerequisites is illustrated by the following examples which, for different reasons have not been useful in determining the stereochemistry of the cyclopropyl–allyl anion transformation.



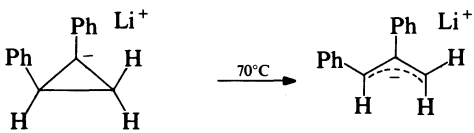
(218) (219$^{=}$) (220$^{=}$) (Ref. 200)



(222) (223$^{=}$) (224$^{=}$) (Ref. 200)



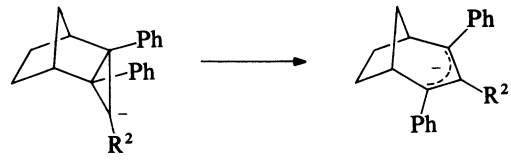
(227) (228^{-}) (229^{-}) (Ref. 202)



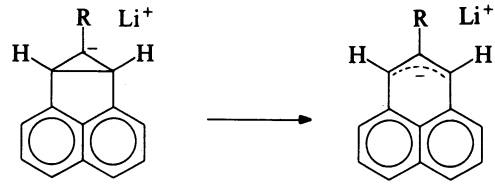
(325^{-}) (326^{-}) (Ref. 251)

Ring-opening reactions in tricyclic systems (e.g. **171**$^{-}$ → **172**$^{-}$) which are likely to occur via a cyclopropyl–allyl anion rearrangement have been discussed in more detail in Section III.C.2.a.

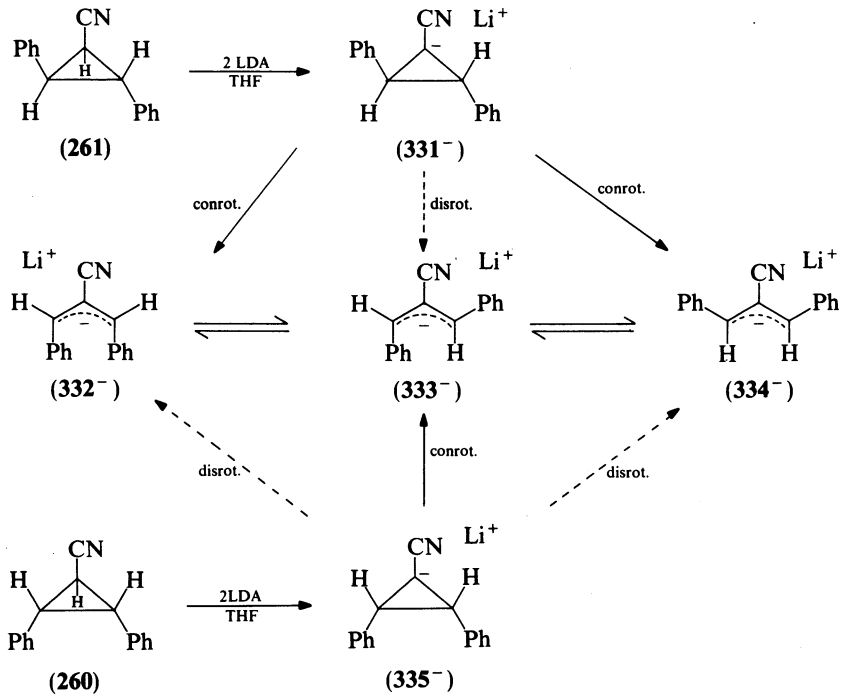
In these systems as well as in the case of the cyclopropyl anions **327**$^{-}$ which gives **328**$^{-}$ slowly at 100°C and **329**$^{-}$ which gives **330**$^{-}$ slowly at 0°C, which were studied by Wittig and coworkers[90a], the ring-opening reactions can not occur in a conrotatory fashion. The slow disrotatory opening of **329**$^{-}$ (R = CN), however, was useful in elaborating a kinetic criterion for the cyclopropyl–allyl anion transformation by the groups of Boche[218a,219]



(171$^-$) (172$^-$)



(327$^-$; R = H) (328$^-$; R = H)
(329$^-$; R = CN) (330$^-$; R = CN)

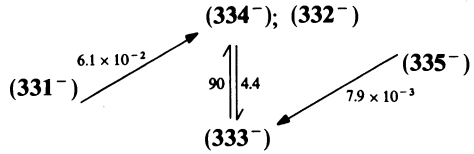


(261) (331$^-$) (332$^-$) (333$^-$) (334$^-$) (260) (335$^-$)

and Ford[200b,c] using in addition the isomeric 2,3-diphenylcyclopropyl nitriles **260** and **261**. Deprotonation of **261** with 2 molar equivalents of lithium diisopropylamide in THF at −30°C led to the *trans*-cyclopropyl anion **331**$^-$ which on warming to 20°C gave mainly the *endo, exo*-ally anion **333**$^-$ besides 4.5% of the *exo, exo*-isomer **334**$^-$ (and less likely *endo, endo*-isomer **332**$^-$) as shown by ^{1}H-NMR spectroscopy and protonation.

The similarly formed *cis*-cyclopropyl anion **335**$^-$ (from **260**) led exactly to the same

result as in the case of **331**$^-$, with **333**$^-$ being formed predominantly. It thus seems that the fast isomerization of the allyl anions **332**$^-$, **333**$^-$ and **334**$^-$ accumulates quickly the thermodynamically most stable isomer **333**$^-$, which prevents the experimental verification of the thermal conrotation by determining the structure of the allyl anions formed in the two ring-opening reactions. That this was indeed the case was confirmed by kinetic studies of the ring-opening and isomerization reactions (Scheme 21).



SCHEME 21. Rate constants for ring-opening reactions of the cyclopropyl anions **331**$^-$ and **335**$^-$ (s^{-1} at 20°C), and of isomerization reactions of the allyl anions **333**ϵ and **334**$^-$ (**332**$^-$) (s^{-1} at 24.5°C)

The ring-opening reaction, e.g. of **331**$^-$ to give **334**$^-$ (and/or **332**$^-$ which is not clear from the available data), is about 1500 times slower than the isomerization of the allyl anion **334**$^-$ (and/or **332**$^-$) to give the more stable **333**[252]. A similar situation obtains for **335**$^-$.

A comparison of the rate constants given in Scheme 21 with the rate constant of the disrotatory ('forbidden') ring-opening reaction in the related Wittig system[90a] **329**$^-$ → **330**$^-$, however, allows the evaluation of a kinetic criterion for the thermal conrotation in the cases of **331**$^-$ and **335**$^-$. At 20°C the following ratios of rate constants are calculated:

$$\frac{k_{331^-}}{k_{329^-}} = 5500; \qquad \frac{k_{335^-}}{k_{329^-}} = 740$$

The 'forbidden' disrotation of **329**$^-$ thus is much slower than the ring-opening reactions of **331**$^-$ and **335**$^-$ which are not hindered to occur in the 'allowed' conrotatory fashion.

The generally slow conrotatory ring-opening reaction of cyclopropyl anions as compared to the fast isomerization of the corresponding allyl anions has been supported by means of MO calculations with the parent anions (Table 31)[219].

TABLE 31. Relative energies (kcal mol^{-1}) of the cyclopropyl–allyl anion transformation and the allyl anion isomerization[219]

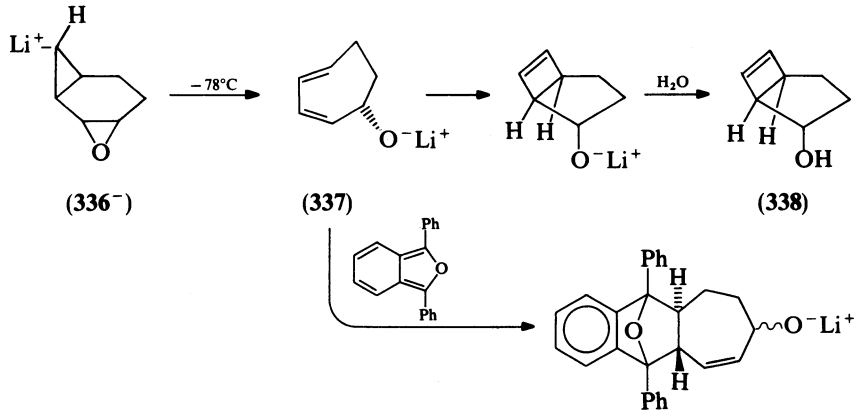
STO-3G	66.7	25.3
4-31G	38.0	27.6

The experimental data obtained with the cyclopropyl anions **331**$^-$ and **335**$^-$, and the allyl anions **332**$^-$, **333**$^-$ and **334**$^-$, are therefore symptomatic of the cyclopropyl–allyl *anion* system.

It is interesting to mention the entirely different situation in the cyclopropyl–allyl *cation* system: the ring-opening reaction is very fast as compared to the isomerization of the allyl cation. In agreement with this situation the disrotatory mode of the cyclopropyl–allyl cation transformation has been 'much easier' to verify[253].

The electrocyclic transformation of the β-lithiocyclopropyloxirane **336**$^-$ also occurs in a conrotatory fashion as suggested by the formation of **338** (after protonation) from the

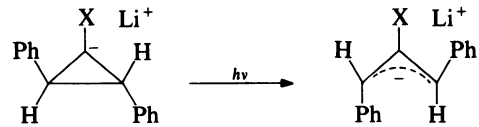
intermediate **337** which has been trapped in a Diels–Alder reaction to give the *trans*-fused adduct **339**[254].



(339)

This ring-opening contrasts sharply with the normally observed stability of cyclopropyllithium compounds with hydrogen at C(1) and alkyl substituents at C(2) snd C(3) as mentioned above. In this electrocyclic transformation combined with a Grob-type heterocyclic fragmentation the ring-opening reactions of both three-membered rings must therefore be concerted[255].

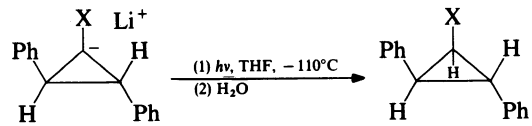
Photochemical cyclopropyl–allyl anion transformations with some of the cyclopropyl anions described above have been observed by Newcomb and Ford[200c] and by Fox[256].



(**331**⁻; X = CN)
(**340**⁻; X = CO_2Me)

(**333**⁻; X = CN)
(**341**⁻; X = CO_2Me)

Thus with the cyclopropyl anions **331**⁻ and **340**⁻ it has been established that the disrotatory mode, as predicted by Woodward and Hoffmann[79], is the preferred one. It is however not clear whether a photochemical cyclopropyl–allyl anion or a thermal cyclopropyl radical ring-opening (the latter caused by photochemical electron ejection) takes place. It has also been realized that systems with X = vinyl or Br (**342**⁻ and **343**⁻, respectively) do not open photochemically[256c].

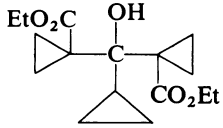


(**342**⁻; X = vinyl)
(**343**⁻; X = Br)

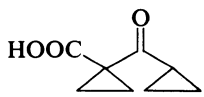
These results have been attributed[256c] to an 'increased ionicity' of the carbon–lithium bond in the case of **331**$^-$ and **340**$^-$ as compared to **342**$^-$ and **343**$^-$. This conclusion is supported by electrochemical measurements and MNDO calculations[257]. A similar conclusion had been reached earlier by Boche and Martens[219] for thermal cyclopropyl–allyl anion transformations.

D. Synthetic Applications

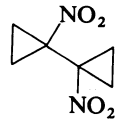
The generation and alkylation of electronegatively substituted cyclopropyl anions, under preparatively useful conditions is not a straightforward procedure. For example, attempts to deprotonate ethyl cyclopropanecarboxylate have led to formation of a Claisen aldol condensation product[197,205a] (**238**; Section IV.B). Although the dianion of cyclopropanecarboxylic acid is capable of reacting with some electrophiles at 20°C[198], it dimerizes rapidly at 50°C to yield **344**[196,197]. Nitrocyclopropane[205a,242a] also undergoes a self-condensation under the influence of strong base to produce **268** and **269**.



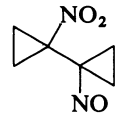
(238)



(344)

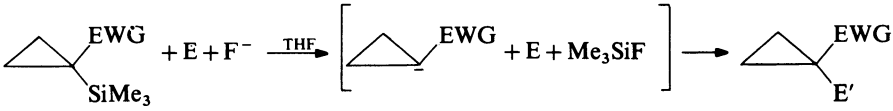


(268)



(269)

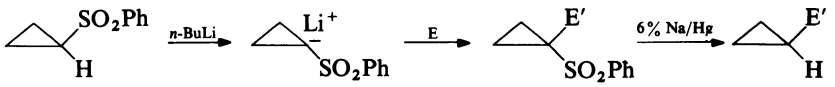
The propensity for self-condensation may sometimes be reduced or eliminated by placing bulky substituents beta to the electron-withdrawing group[216] or even attached to the electron-withdrawing group[206]. The latter methodology has been elaborated very recently by Seebach and coworkers[205b] (see also Section IV.B.1.a). Cation chelating substituents in the beta positions are also effective in reducing self-condensation[209]. A



(345) (346) (347)

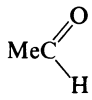
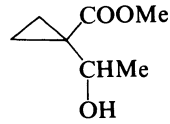
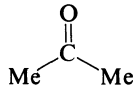
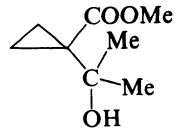
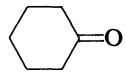
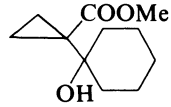
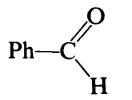
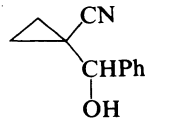
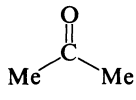
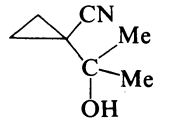
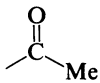
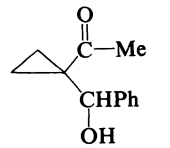
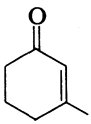
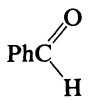
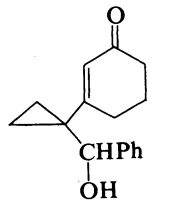
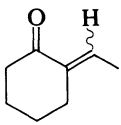
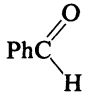
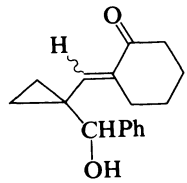
method, developed by Paquette and coworkers[258], provides a means for avoiding the problem of self-condensation. It takes advantage of the fluoride ion desilylation of α-trimethylsilylcyclopropanes containing an electron-withdrawing group (EWG) in the α-position (**345**). The desilylation produces, *in situ*, an α-anion **346** which can condense with an electrophile E that is already present in solution to yield **347**. The overall reaction is depicted above and Table 32 records some results.

If the electron-withdrawing group is such that self-condensation does not occur then the anion can be generated in the normal manner. Thus, the anion **349** of cyclopropyl phenyl sulfone (**348**) can be readily prepared by treatment of the parent compound with *n*-butyllithium at 0°C in THF. The anion has been shown to condense in excellent yield with aldehydes, ketones, methyl iodide and allyl and benzyl bromides[259] to yield **350**. The



(348) (349) (350) (351)

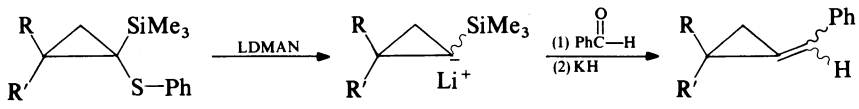
TABLE 32. Desilylation and condensation reactions

EWG in **345**	Fluoride source	E	Product	Yield (%)
COOMe	TBAF[a]			90
	TBAF			68
	TBAF			45
CN	BTAF[b]			83
	BTAF			55
	BTAF			63
	BTAF			73
	BTAF			45

[a] Tetrabutylammonium fluoride.
[b] Benzyltrimethylammonium fluoride.

phenyl sulfone group can be readily removed by reduction with sodium amalgam[259] to produce desulfurized **351**.

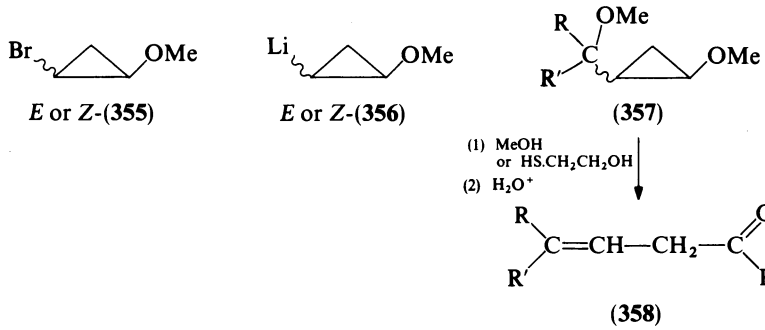
1-(Lithio)cyclopropylsilanes are useful intermediates since they can readily be transformed to synthetically useful alkylidene and allylidene derivatives when used in the Peterson olefination[260]. Treatment of 1-phenylthio-1-trimethylsilylcyclopropanes (**352**) with lithium 1-(dimethyl-amino)-naphthalenide (LDMAN) produces 1-lithio-1-(trimethylsilyl)-cyclopropanes (**353**) which can be condensed with a variety of carbonyls[260,261]. The products are converted by elimination to the exocyclic olefin (**354**).



(**352**) (**353**) (**354**)

The formation of carbon–carbon bonds by means of three carbon homologating agents (d^3 synthons)[262] can provide a useful and desirable methodology for the preparation of *inter alia*, α,β- and β,γ-unsaturated aldehydes.

The d^3-synthons that lead to the formation of β,γ-unsaturated aldehydes (**358**) are *E*- and *Z*-2-methoxycyclopropyllithium[263] (**356**) which can be readily prepared, at $-78°C$, by treatment of *E*- and *Z*-2-methoxycyclopropyl bromide (**355**) with *t*-butyllithium. The lithium reagent is condensed with a carbonyl compound to yield the corresponding cyclopropylcarbinol which is converted to its mesylate derivative **357**. The mesylates,



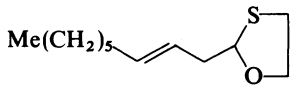
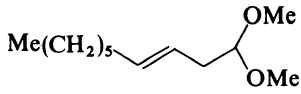
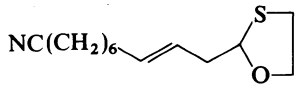
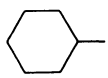
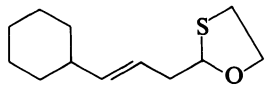
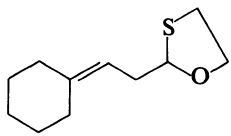
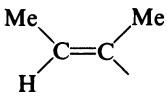
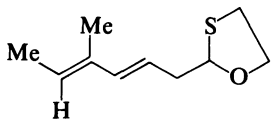
E or *Z*-(**355**) *E* or *Z*-(**356**) (**357**)

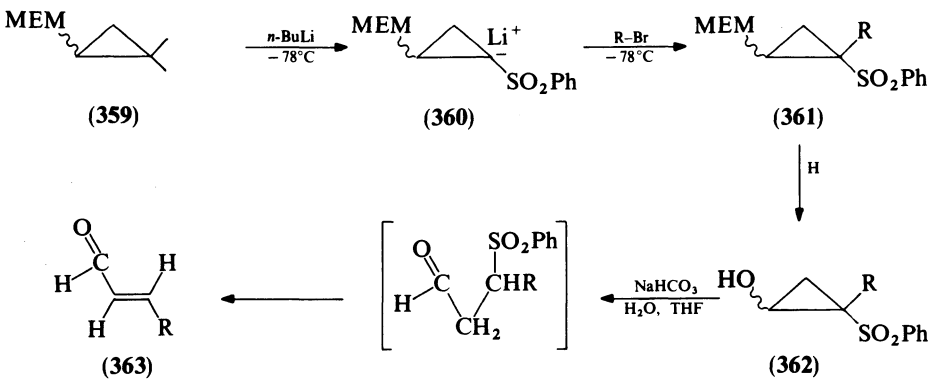
(**358**)

which are not isolated, are solvolysed in methanol or 2-mercaptoethanol to yield the corresponding acetals or hemithioacetals. The latter can be especially useful because, although relatively acid resistant, they are readily hydrolyzed under neutral conditions with mercuric ion assistance or via the *S*-methyl sulfonium derivative. Examples for the process are given in Table 33.

The anion of 2-(methoxyethoxymethoxy)cyclopropyl phenyl sulfone (methoxyethoxymethoxy = MEM) is a d^3-synthon for α,β-unsaturated aldehydes[264]. The anion is readily formed by treating 2-(MEM)cyclopropyl phenyl sulfone (**359**) with *n*-butyllithium in THF at $-78°C$. Treatment of the anion **360** with aliphatic primary bromides or allyl bromide produces the alkylated sulfone **361** in very good yields. Hydrolysis of the MEM-protecting group was readily performed by treatment with aqueous tetrafluoroboric acid to furnish the cyclopropanol sulfone (**362**). Treatment with aqueous sodium bicarbonate produced the corresponding aldehydes **363** in 70–90% yields.

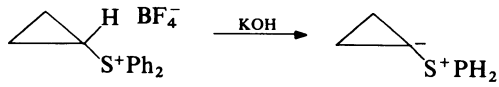
TABLE 33. β,γ-Unsaturated aldehydes by three carbon homologation

R	R′	Acetal or hemithioacetal	(% Yield)	β,γ-Unsaturated aldehyde (% Yield)
$Me(CH_2)_5$	H		77	93
$Me(CH_2)_5$	H		97	96
$NC(CH_2)_6$	H		82	93
	H		72	91
$(CH_2)_5$			81	95
	H		61	67



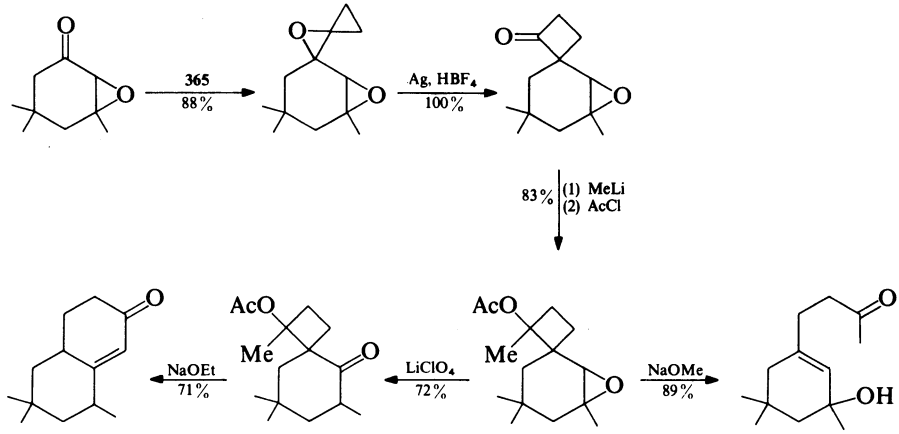
Although the anion is used as a means of derivatizing the sulfone the key step to this method is the generation of a homoenolate anion and its subsequent rearrangement. The subject of homoenolate anions and their synthetic applications has been extensively reviewed elsewhere[265].

Cyclobutanones have become very useful intermediates for synthesis since their introduction by Trost as a means of secoalkylation[266]. The key element in the synthesis was diphenylsulfonium cyclopropylide (**365**) which is generated from its precursor diphenylcyclopropylsulfonium fluoroborate (**364**) by treatment with potassium hydroxide.



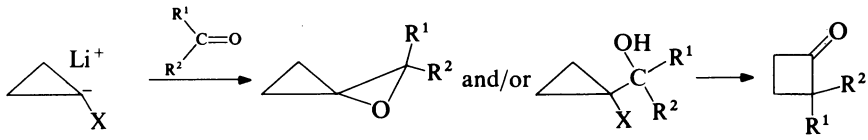
(**364**) (**365**)

The use of the ylide in secoalkylation and secoalkylative annelation is shown in Scheme 22[266a,b]. Cyclobutanones can also serve as precursors to five-[267], six-[268] and eight-membered[269] rings as well as a variety of highly functionalized acyclic[266b,270] molecules.



SCHEME 22. Secoannelation and secoalkylation

Besides ylids, carbenoids (**366**) can also be used since they too can condense with ketones to yield oxaspiropentanes (**367**) or heteroatom-substituted cyclopropylcarbinols (**368**), both of which rearrange to cyclobutanone derivatives (**369**) under acid catalysis. The 1-ethoxycyclopropyllithium is the carbenoid reagent of choice because of its ease of

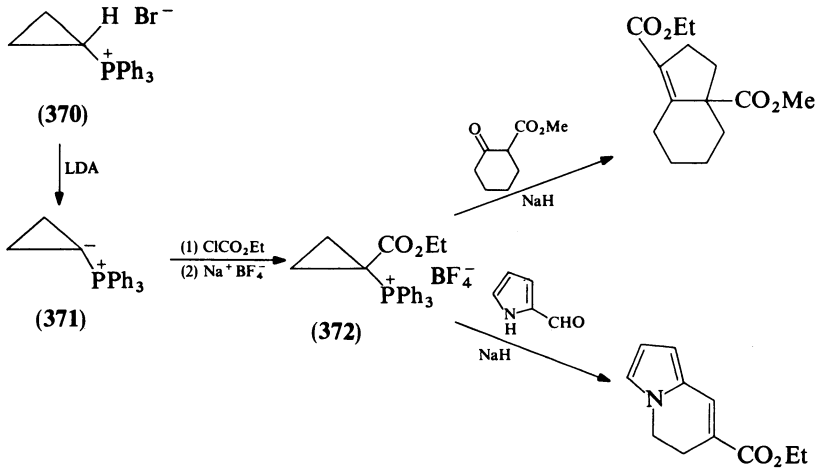


(**366**) (**367**) (**368**) (**369**)

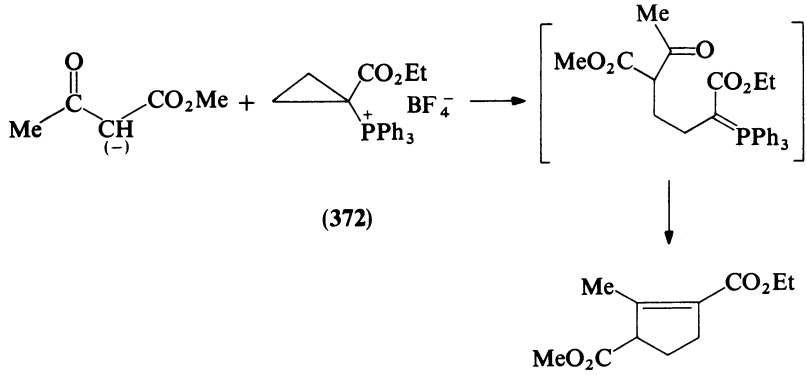
X = Br[271], SPh[272], SePh[273], OMe[274], OEt[275]

preparation and condensation with carbonyls. Also the rearrangement to the cyclobutanone derivatives is greatly accelerated and cleaner[274,275].

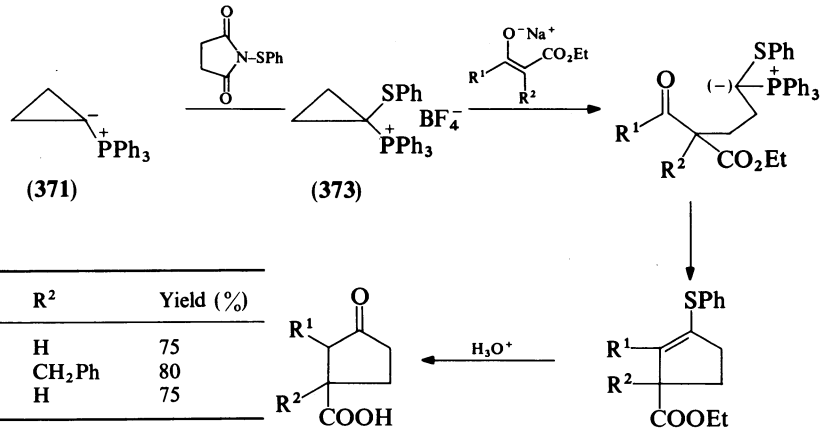
The ylid **371** prepared by treating cyclopropyltriphenylphosphonium bromide (with lithium diisopropylamide (LDA) produces a useful synthon on reaction with ethyl chloroformate[276]. The fluoroborate salt (**372**) was shown to be an excellent reagent for cycloalkenylation of carbonyl compounds. The ylid was used successfully in the total synthesis of Spirovetivanes[277].



The reaction involves nucleophilic attack at the beta cyclopropyl carbon and cleavage of the cyclopropyl ring which produces an ylid that condenses intramolecularly with the carbonyl moiety.



Replacing the carboethoxy group by a thiophenyl group in the cyclopropyltriphenylphosphonium salt generates a new synthon **373** which is useful in cyclopentanone synthesis[278].



R^1	R^2	Yield (%)
Me	H	75
Me	CH_2Ph	80
Ph	H	75

V. ACKNOWLEDGEMENT

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CHAPTER 13

Rearrangements involving the cyclopropyl group

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I. INTRODUCTION

The cyclopropane chemical reactivity, which closely resembles that of an olefinic double bond, stems from the electronic properties of this three-membered carbocycle[1]. Effectively, cyclopropyl and olefinic groups interact with neighbouring π-electron systems and p-electron centres; they both add acids, halogens and ozone, undergo catalytic hydrogenation and cycloaddition, form metal complexes, etc.

Formally a cyclopropane is a small ring with double bond character which, more specifically, can undergo ring-opening, $C_3 \rightarrow C_4$ and $C_3 \rightarrow C_5$ ring expansions and is also involved in the $C_4 \rightarrow C_3$ ring contraction of four-membered cyclic systems. This chapter is concerned with such rearrangements.

Computer's investigation of the chemical data bases (Chemical Abstracts) covering the period 1966–1984, dealing with the term CYCLOPROP (for cyclopropane and (or) cyclopropyl) gave 10 799 items. Consequently, only the main features of this topic are discussed in order to show the considerable efforts which have been and which are still currently devoted to the study of the challenging cyclopropane chemistry.

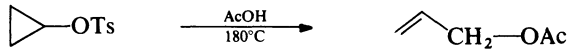
A book concerning the chemistry of cyclopropane derivatives was published in 1971[2], so the aim of this chapter is to review, up to now, the peculiar recent aspects of the rearrangements involving the cyclopropyl and cyclopropenyl groups.

II. CYCLOPROPANE RING-OPENINGS

Cyclopropane derivatives can undergo solvolytic, electrophilic, anionic, nucleophilic as well as thermal, photolytic and metal-induced ring-openings. In this paragraph we underline particularly the specific ring cleavage of halo- and siloxycyclopropanes which now provides convenient new synthetic pathways. The reductive ring-opening by hydrogenation[2] is not included in this chapter.

A. Solvolytic

Roberts and Chambers were the first to observe that cyclopropyl tosylate (**1**) is extremely inert, requiring 180 °C for acetolysis. The product of the reaction is not cyclopropyl acetate, but rather allyl acetate (**2**) (equation 1)[3].

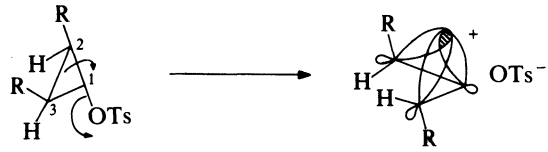


(1) (2) (1)

It was shown that the cyclopropyl cation is not an intermediate but that ring-opening occurs simultaneously with loss of tosylate[4]. Prediction[5] and experiments[6] showed that for this electrocyclic transformation, susceptible to treatment by the Woodward–Hoffmann rules[5], the substituents *cis* to the leaving group rotate *inwardly* and substituents *trans* to the leaving group rotate *outwardly* (equation 2).

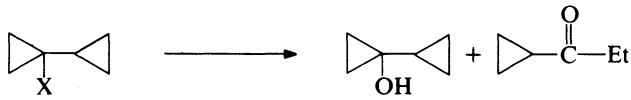
(2)

Kinetic and stereochemical data have fully confirmed that the electrons of the C(2)–C(3) bond interact with the rear of the developing orbital on C(1) (equation 3)[7].



(3)

This concerted ionization and disrotatory ring-opening of cyclopropyl substrates has been an area of continuing interest[8]. It can be prohibited by steric[9] or conjugative interactions[10]. For instance, 1-cyclopropylcyclopropyl chloride (**3a**)[11] or tosylate (**3b**)[10] lead to unrearranged solvolysis products, i.e. 1-cyclopropylcyclopropanol (**4**), and to cyclopropylethyl ketone (**5**) arising from homoketonization (equation 4).

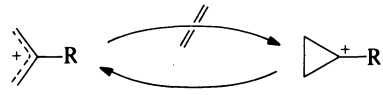


(3)		(4)	(5)	(4)
a; X = Cl	H_2O. Ag^+	—	65%	
b; OTs	aq. acetone	63%	24%	

The solvolysis product of alkyne-substituted 1-ethynyl cyclopropyl tosylates (**6**) appeared to be strongly dependent upon the nature of the substituent R of the triple bond. So, stabilization of the intermediate cyclopropyl cation (**7**), by delocalization of the positive charge over the three carbons of the mesomeric propargyl–allenyl system, entails a powerful electron-releasing substituent R: effectively, when R = *p*-anisyl, the ring-opening of the cyclopropyl cation was totally suppressed (equation 5)[12].

(6) (7) (8) (5)

For other examples of survival of the cyclopropane ring in such reactions, see Ref. 13. The ^{13}C–deshielding parameter of a cyclopropyl cation ($\Delta\delta^{13}C = 150$ ppm) has been reported[14]. However, although theoretically, electron-releasing substituents might render 1-substituted cyclopropyl cations more stable than their 2-substituted allyl counterparts[15], the expected ring closure of 2-substituted allyl cation (**9**) has not been observed experimentally (equation 6)[16].

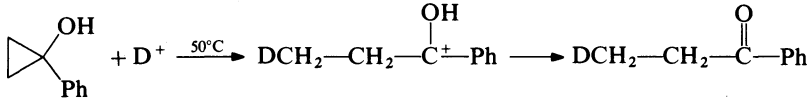


(6)

(**9**)

B. Electrophilic

In general, cyclopropanes open under the influence of acidic reagents to form the most stable carbenium ion, which then may rearrange, eliminate in one or several directions, react with solvent, or give rise to any one of a number of products[2, 17]. Still more readily, cyclopropanols (or their ethers and esters) react with acids, mercuric salts and halogenating agents. The hydroxyl group, by virtue of its ability to stabilize an adjacent positive charge, controls and facilitates the ring-opening so that one, or at most two, products are formed. The intermediate carbenium ion, by loss of the hydroxyl proton, is then converted completely to stable ketonic products. For instance, 1-phenylcyclopropanol (**10**) is converted quantitatively to propiophenone upon treatment with 1N hydrochloric acid in 50 : 50 dioxane–water solution at 50 °C; if a deuterio acid is used, a single β-deuterium atom is introduced into the ketone (equation 7)[6, 18].



(**10**) (7)

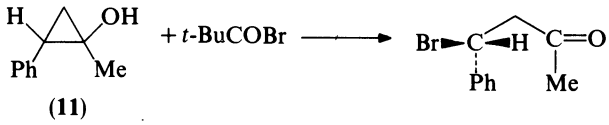
Kinetic study has shown that appreciable positive charge develops on the 1-carbon in the transition state. The electrophilic proton attacks the C(1)–C(2) bonding electrons, probably at the edge of the ring[18, 19]. Opening of optically active *trans*-1-methyl-2-phenylcyclopropanol (**11**) gives optically active 4-phenyl-2-butanone with *retention* of configuration (equation 8)[18].

(**11**) (8)

However, one example of ring-opening of a cyclopropylmethyl ether with *inversion* is known[20].

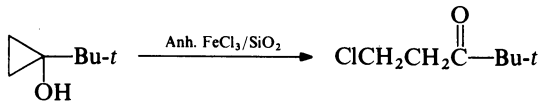
The reaction is of a second order, i.e., first order in both the reacting alcohol and the acid, and was classified according to the Hughes–Ingold terminology as a S_E2 reaction[18]. Cyclopropanols and derivatives react readily with mercuric acetate in either acetic acid or methanol[21]. The stereochemistry of the resultant organomercurial depends strongly upon the substitution pattern of the substrate; attack occurs most readily on the least substituted bond. Compared to the acid-induced reaction, the mercuric acetate ring-opening is highly sensitive to steric hindrance. Cyclopropanols react also with halogenating agents. With bromine or chlorine the corresponding hydrogen halide is a by-product of the opening and

may compete with the halogen as the electrophile; for this reason *t*-butyl hypohalite and *N*-bromosuccinimide were used. Their reactions gave a simple haloketone with *inversion* of configuration (equation 9)[18, 22].



(11) (9)

Cyclopropanols are also easily oxidized by ferric chloride either in ether[6, 23] or when dispersed on silica gel in the absence of any solvent (equation 10)[24].

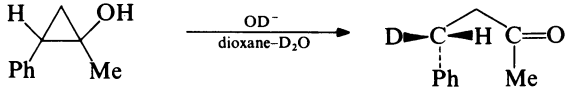


(10)

Other electrophilic reactions of cyclopropanols have been reviewed[6].

C. Anionic

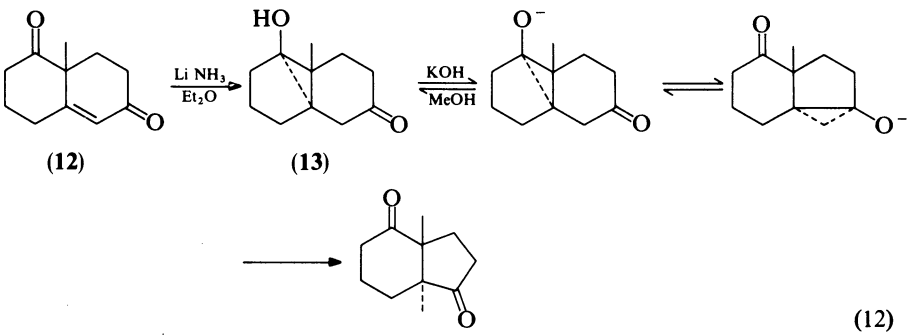
In dilute basic solution, cyclopropanols readily undergo ring-opening toward the ring carbon atom which can best stabilize a negative charge[6, 25]. In dioxane–D_2O the ring-opening of a phenyl-substituted system proceeds with *inversion* of configuration at the benzylic carbon atom (equation 11)[6a, b].



(11) (11)

However, predominant *retention* using potassium *t*-butoxide in *t*-butyl alcohol and *inversion* using ethylene glycol and its sodium salt have been observed[6c]. The high stereospecificity observed in the cyclopropanol opening seems to argue against a 'free carbanion'; an acid catalysed S_E2 reaction would be involved[26].

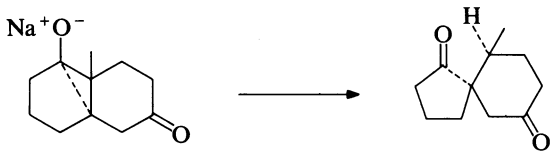
The unexpected rearrangement of the cyclopropanol (**13**) derived from the Wieland–Miescher ketone (**12**), has been rationalized in terms of equilibrating cyclopropylalkoxide ions and solvent capture at carbon with ring-opening (equation 12)[27]. (A similar acid-catalysed isomerization can also take place.)



(12) (13)

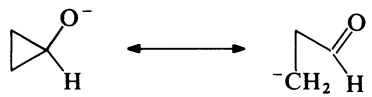
(12)

However, the normal course for base-catalysed ring-opening of the alcohol (**13**) could be effected by converting the substrate to its sodium salt (**14**) (by NaH) followed by quenching with methanol; the spiro ketone (**15**) obtained in this reaction results from *retention* in the protonation step (equation 13)[27].



(**14**) (**15**) (13)

Cyclopropanol may be regarded as the simplest homoenol, the cyclopropylalkoxide ion structure is one of the pair of hybrid structures which constitute the parent homoenolate ion (equation 14).

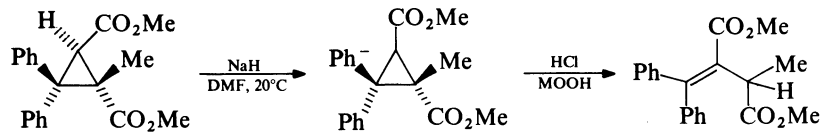


(14)

Attempts have been made to generate a carbanion center β to a carbonyl group in systems capable of closing into the cyclopropyl alkoxide[28,29].

The base-induced rearrangement of α-haloketones, known as the Favorskii rearrangement, proceeds in general through cyclopropanone intermediates and subsequent ring-opening[30]. The acid- and base-induced ring-opening of cyclopropanones[30,31] and 1-alkoxycyclopropanols, i.e. cyclopropanone hemiacetals[32] have been reviewed.

Several ring-openings of bicyclic cyclopropyl anions to aromatic anions have been described[33]. An electron-attracting substituent acidifies a cyclopropyl hydrogen and facilitates deprotonation to give a carbanion. Substituents that stabilize negative charge at the two remaining carbons, which become the terminal centres of the allyl anion, are expected to aid the ring scission. Thus, on reaction of *trans*-dimethyl-1-methyl-3,3-diphenylcyclopropane-1,2-dicarboxylate (**16**) with sodium hydride in DMF at 20 °C and acidification with methanolic hydrogen chloride, an allylic diester (**17**) was obtained (equation 15)[34].



(**16**) (**17**) (15)

Conrotation was predicted for the thermal ring-opening of the cyclopropyl anion to the allyl anion[5].

Base-induced formation of α-cyclopropylcarbanions leads also to ring-opened products[2].

D. Nucleophilic

Most of the nucleophilic openings of cyclopropanes have involved two geminally placed activating groups, usually esters. Thus, cyclopropanedicarboxylates (**18**) have undergone

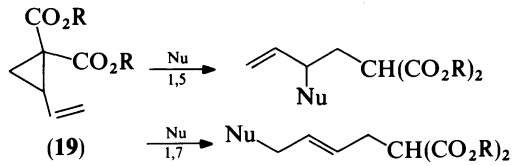
ring-opening with amines, mercaptans, enamines, cuprates, malonate anion and other nucleophiles (equation 16)[35].

(16)

(18)

The reaction conditions have been quite vigorous, reflecting the difficulty of cleaving the strained carbon–carbon single bond. The bond which is cleaved is the one best situated for simultaneous overlap with both carbonyl activating groups.

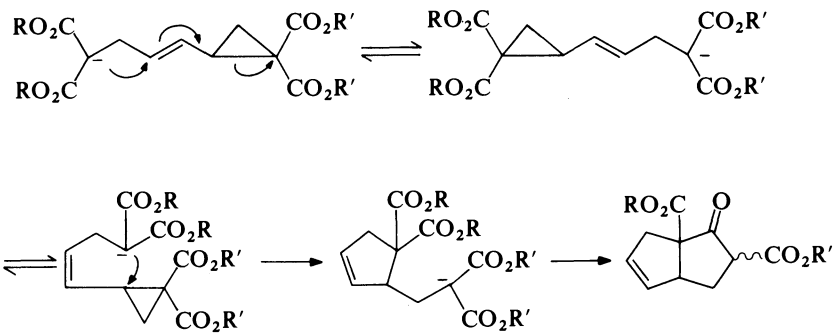
Activated vinylcyclopropanes (**19**) are an interesting class of ambident electrophiles; two modes of ring-opening, referred to as 1,5 and 1,7 attacks, have been observed (equation 17)[36].



(17)

(19)

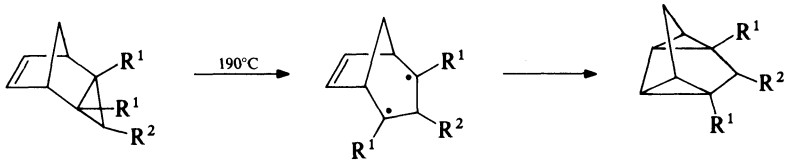
An elegant route to 11-deoxyprostaglandins uses a 1,5 attack of an enolate on such an activated cyclopropane[37]. The ring-opening of activated cyclopropanes by intramolecularly situated nucleophiles has also been achieved[35]. An interesting case of intramolecular 1,7 attack on an activated vinylcyclopropane was observed upon treatment with dimsyl sodium-Me_2SO at 90°C (equation 18)[38].



(18)

E. Thermal

Thermally ring-opened cyclopropanes undergo intramolecular cycloaddition to π bonds. Thus, on heating at 190 °C for 1.5 h tricyclo[3.2.1.$0^{2,4}$]oct-6-enes (**20**) rearrange to tetracyclo[3.3.0.$0^{2,8}$.$0^{4,6}$]octane derivatives (**21**) (equation 19)[39]. (For related rearrangements see Ref. 40.)

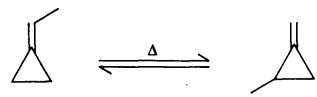


(20) (21) (19)

R^1 = Ph
R^2 = Ph, CO_2Me

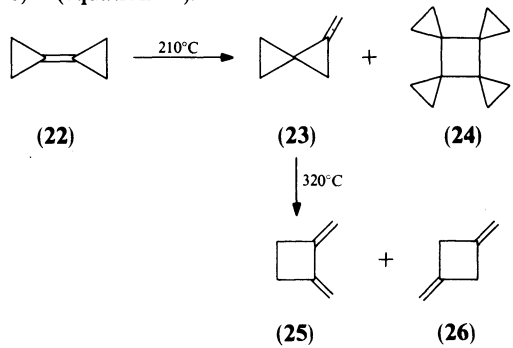
The mechanism of this thermal valence isomerization was formulated as proceeding by an intermediate diradical. Extended Hückel calculations have shown that the opening of the *endo* compounds into diradicals is a symmetry-forbidden process, in contrast to the ring opening of the *exo* derivatives[39].

Trimethylenemethane has been postulated to be the reactive intermediate in a number of reactions involving the ring-opening and rearrangement of methylenecyclopropanes[41]. In fact, methylenecyclopropanes are known to undergo degenerate thermal rearrangements. An early example, the ethylidenecyclopropane–methyl methylenecyclopropane interconversion, is shown in equation 20[42].



(20)

Since the discovery of the thermal rearrangement of the Feist's ester[43], numerous examples of the methylenecyclopropane rearrangement have been reported[41]. In particular, cyclopropylidenecycloalkanes lead to methylenespiro[2.*n*]alkanes[44]. For instance, on heating to 210 °C biscyclopropylidene (**22**) undergoes rearrangement to methylenespiropentane (**23**) and dimerization into tetracyclopropylidene (**24**)[45]; on further heating to 320 °C, methylenespiropentane (**23**) rearranges to 1,2- and 1,3-dimethylenecyclobutane (**25** and **26**)[44] (equation 21).



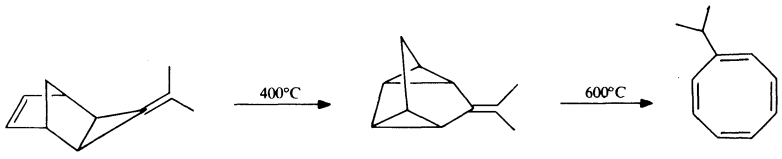
(**22**) (**23**) (**24**)

(**25**) (**26**) (21)

Non-planar trimethylenemethane was hypothesized as the key intermediate of these thermal isomerizations[44].

Geminal dichloromethylenecyclopropanes, readily available from the addition of dichlorocarbenes to allenes, undergo related thermal reorganizations[46].

On flash thermolysis at 400°C[47] or heating at 150°C for 20 min[47,48], 3-isopropylidenetricyclo[3.2.1.$0^{2,4}$]oct-6-ene (**27**) led to 3-isopropylidenetetracyclo [3.3.0.$0^{4,6}$.$0^{2,8}$]octane (**28**) (equation 22).

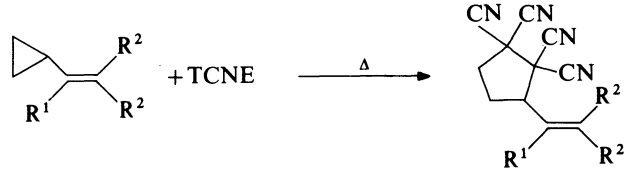


(22)

(27) (28) (29)

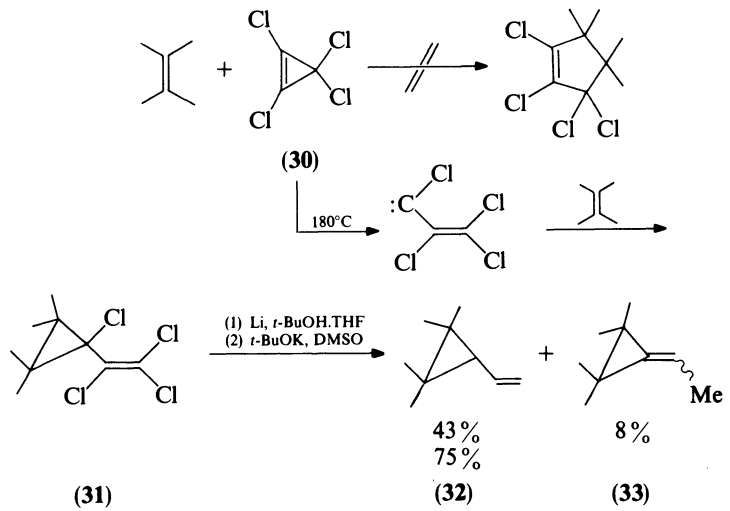
This thermal rearrangement, which is the formal result of a σ 2S + π 2S cycloaddition is consequently orbital symmetry forbidden[5]. Rather, an homolytic cleavage of the cyclopropane bond, giving rise to a trimethylenemethane, would be involved. This rearrangement was the first reported intramolecular trapping of a trimethylenemethane by a double bond (for a related intermolecular trapping of trimethylenemethane by butadiene see Ref. 49). On further heating to 600°C, the main product obtained was isopropylcyclooctatetraene (**29**) (equation 22)[47].

In analogy to the π^2–π^2 cycloaddition of electron-rich alkenes with electron-deficient olefins[50], cycloadditions between donor–acceptor pairs of cyclopropanes and unsaturated compounds have been obtained. They include for instance the cycloaddition of substituted cyclopropanes with ethylene-tetracarbonitrile (TCNE), (equation 23[51]). [10]Paracyclophadienes have been obtained from the reaction of tetrasubstituted 1,2-dicyclopropylethylenes with TCNQ[52].



(23)

Attempted thermal cycloaddition of tetrachlorocyclopropene (**30**) to olefins did not lead to the expected five-membered ring derivatives but gave in high yields 1-chloro-1-(trichlorovinyl)cyclopropane derivatives (**31**), via the intermediacy of a tetrachlorovinylcarbene (equation 24)[53].



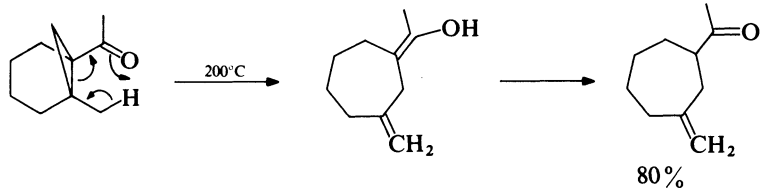
(24)

(31) (32) (33)

The product can be reductively dechlorinated with lithium in THF–*t*-butanol to give a mixture of vinylcyclopropane (**32**) and ethylidenecyclopropane (**33**), in 43 and 8% yield, respectively. Then, by treating the reaction mixture with potassium–*t*-butoxide in DMSO the vinylcyclopropane (**32**) can be obtained in 75% overall yield[53].

This sequence offers also a useful method for the preparation of variously substituted cyclopropylalkynes[54]. (For synthetic uses of this new building block, see Ref. 1c.)

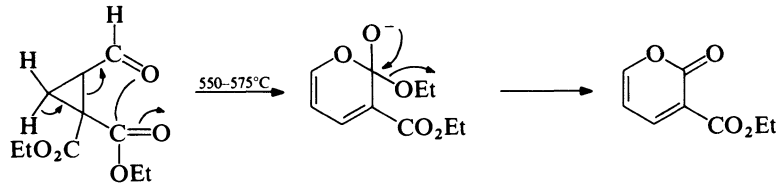
An efficient method for the preparation of functionalized seven-membered rings involves the cleavage of the internal bond of a bicyclo[4.1.0]heptane moiety by a thermal homo[1,5]hydrogen shift or enolene rearrangement[55] (equation 25).



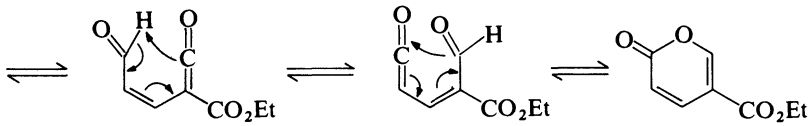
(25)

This ring expansion procedure was extended to the preparation of a functionalized hydroazulene skeleton[56].

A 5-ethoxycarbonyl-2-pyrone (**36**) has been obtained on heating 2,2-diethoxycarbonylcyclopropanecarboxaldehyde (**34**) at 550–575°C, through the intermediacy of 3-ethoxycarbonyl-2-pyrone (**35**) (equation 26)[57].



(**34**) (**35**) (26)



(**36**)

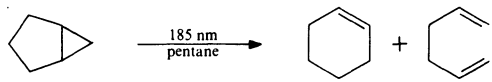
Cyclopropyl radicals generated in solution by thermolysis of *t*-butylcyclopropaneperoxycarboxylates undergo favoured disrotatory ring-opening into allyl radicals[58].

F. Photolytic

Photochemical studies of cyclopropane derivatives in solution have concerned mainly molecules in which a chromophore capable of absorbing at wavelength above 200 nm is attached to the ring. The principal reaction is the cleavage of one bond to give a diradical. Cyclopropane and alkylcyclopropanes have been studied in the gas phase at 147 nm or

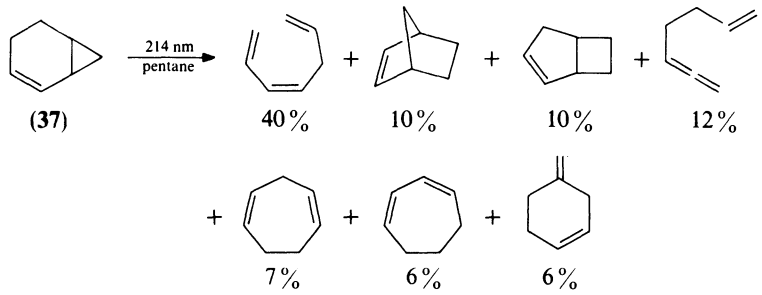
less. The principal reaction under these conditions is a fragmentation into a carbene and an olefin[59].

However, on irradiation in pentane solution at 185 nm (6.7 eV) bicyclo[3.1.0]hexane gives products which formally correspond to the cleavage of one or two bonds of the cyclopropane ring (equation 27)[59a].



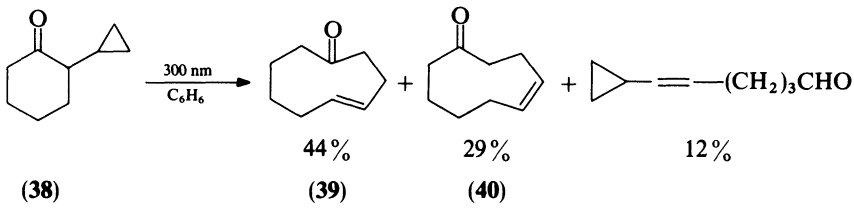
(27)

In contrast to the singlet photobehaviour generally observed for aliphatic cyclopropanes, the product mixture observed upon direct irradiation (214 nm, pentane solution) of 2-norcarene (**37**) reveals that this system is unusual in many respects (equation 28)[59c].



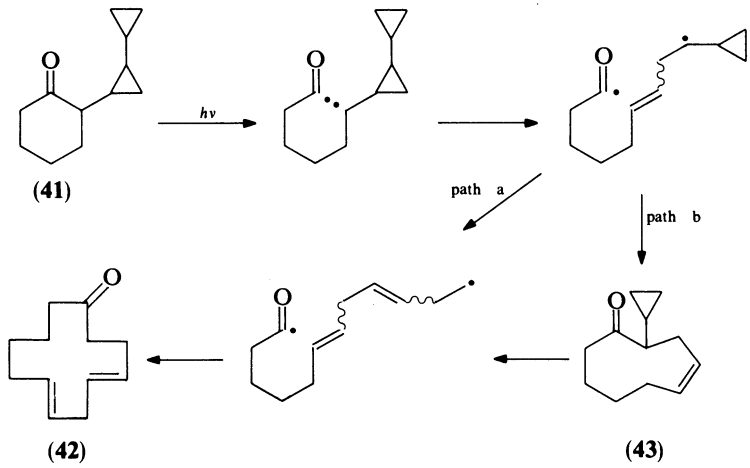
(28)

2-Cyclopropylcycloalkanones (**38**) undergo three-atom photochemical ring expansion into a mixture of *trans* and *cis* cyclonon-4-enones **39** and **40** (equation 29)[60].



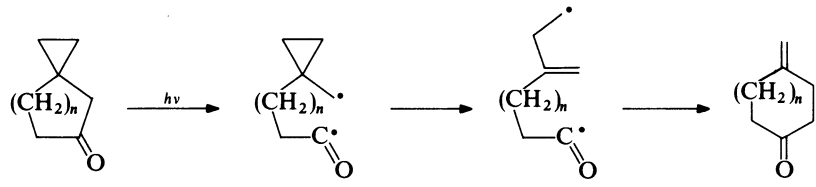
(29)

On the other hand, 2-(2-cyclopropylcyclopropyl) cycloalkanones (**41**) undergo six-atom photochemical ring expansion upon irradiation at 293 nm (equation 30)[61]. The rearrangement produces a mixture of cyclododecadienone (**42**) and 2-cyclopropylcyclononenone (**43**); the corresponding saturated cyclanones have been obtained after catalytic hydrogenation (charcoal Pd) in 48 and 16% yields, respectively. In order to determine qualitatively whether the six-atom ring-expanded products arose by way of a one-photon process (path a) or by two consecutive three-atom ring expansions or a two-photon process (path b) the photolysis was stopped at low conversion. The composition of the reduced photoproduct indicates that the six-atom ring-expanded product is a primary photoproduct[61].



(41) (42) (43) (30)

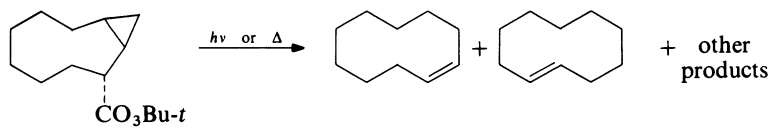
Irradiation of non-conjugated spiroketones (**44**) in hexane affords 4-methylenecycloalkanones (**45**) as ring enlargement products (equation 31)[62].



(44) (45) (31)

The cyclopropane ring is cleaved via the induced ring-opening of a cyclopropylcarbinyl radical to form a diradical which in turn cyclizes intramolecularly to afford the reaction product.

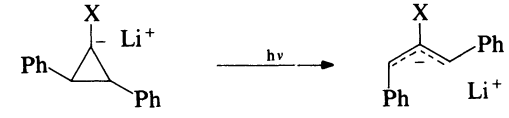
Photolytic and thermal (100°C) decompositions of *t*-butyl *anti*-bicyclo[7.1.0]decane-2-percarboxylate (**46**) were investigated in order to test the behaviour of the corresponding radical (equation 32).



(46) (47) (48) (32)

Complex mixtures were obtained and the formation of both *cis* and *trans* cyclodecenes (**47** and **48**) in a 3 : 1 ratio indicates that, contrary to the cation (*vide infra*, equation 71), the cyclopropylcarbinyl radical does not give a stereospecific ring expansion[63].

Cyclopropyllithiums (**49**) undergo photochemical ring-opening at low temperatures by a net disrotatory pathway (equation 33)[64].



(33)

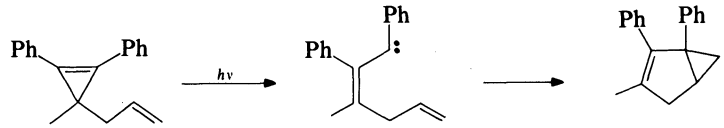
X = CN, CO_2Me

(49)

The reverse photoreaction, i.e. the photocyclization of cinnamylmagnesium bromide to the corresponding cyclopropylmagnesium bromide, has also been described[65].

Bromine atoms, generated by irradiation at wavelengths above 310 nm, react with 1,2-diarylcyclopropanes in CCl_4 to yield 1,3-diaryl-1,3-dibromopropanes[66].

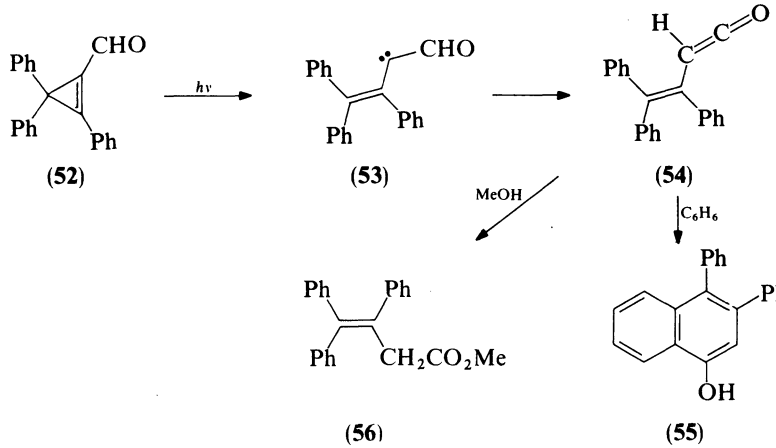
Cyclopropene derivatives have been found to undergo a wide array of novel photochemistry[67]. The photobehaviour is markedly dependent on the substituent groups present and the multiplicity of the excited state involved. Singlet states generally react by σ-bond cleavage to give products which are explicable in terms of the chemistry of vinylcarbenes, while triplet states generated by sensitization techniques give products in which the three-membered ring has been retained[68]. For instance, direct irradiation of 3-allyl-3-methyl-1,2-diphenylcyclopropene (**50**) afforded 1,2-diphenyl-3-methylbicyclo[3.1.0]hex-2-ene (**51**) as the exclusive photoproduct (equation 34)[69].



(34)

(**50**) (**51**)

Irradiation of 2,3,3-triphenyl-1-cyclopropenylcarboxaldehyde (**52**) led to a naphthol derivative (**55**) in benzene or to an allylic ester (**56**) in methanol.

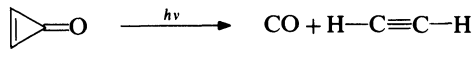


(**52**) (**53**) (**54**) (35)

(**56**) (**55**)

The reaction proceeds through a vinylketene (**54**) formed via a vinylcarbene (**53**) the product of ring-opening of the cyclopropene ring. Then, the ketene undergoes intramolecular cycloaddition in benzene or is trapped by methanol (equation 35)[70].

Photolysis of cyclopropenone (**57**) leads to cleavage of the 1,2 bond and to elimination of carbon monoxide (equation 36)[71].



(**57**) (36)

Some other photochemical isomerizations of cyclopropane derivatives have been reviewed[72].

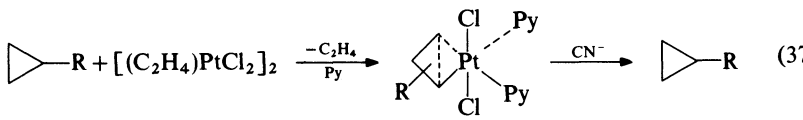
G. Metal-induced

The transition metal promoted rearrangements of small ring organic molecules have received intense examination[73]. A variety of unexpected and unusual rearrangements have been described and a number of cyclopropane–transition metal complexes have been isolated and characterized[73].

The description of organometallic bonding to the cyclopropane σ bonds possessing high p-orbital character is composed of two parts. The σ bond is formed by electron donation from the carbon–carbon bond into an empty metal orbital. Then, the metal is capable of back donation into a relatively low lying σ^* orbital of the hydrocarbon. Thus, the description of the interaction of three-membered rings with transition metals follows closely the description of olefin–metal interaction. However, because the σ^* will generally be of higher energy than the analogous π^* orbital, back donation should be less important than in the olefinic case[73].

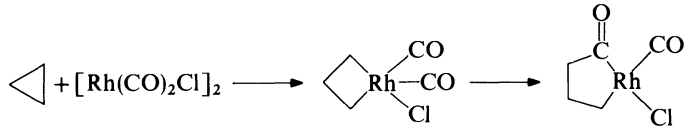
σ bond π bond

This similarity between cyclopropane and olefin was first illustrated by the displacement of ethylene from $[(C_2H_4)PtCl_2]_2$ with various substituted cyclopropanes (equation 37)[74]. The reaction was found to depend markedly on the electron-donor capacity of the cyclopropane ring[75, 76].



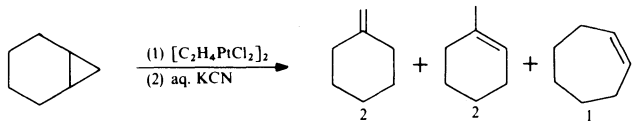
(37)

With electron-rich cyclopropanes, addition of pyridine yields stable metallocyclic complexes, from which cyclopropanes could be regenerated upon treatment with aqueous potassium cyanide[76]. This and the related reaction of cyclopropane with tetracarbonyldichlorodirhodium $[Rh(CO)_2Cl]_2$ which yields rhodacyclopentanone (equation 38) have become the precedents for a wide range of insertions and isomerizations of strained compounds[73].



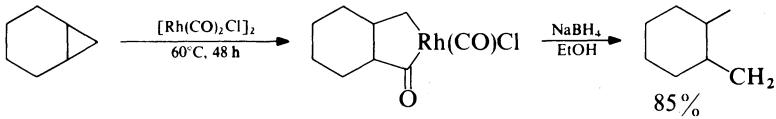
(38)

Bicyclo[4.1.0]heptane (**58**) behaved similarly. When heated with dichloro(ethylene)platinum in ether at reflux for 1 h an orange complex was formed which underwent decomposition upon treatment with aqueous potassium cyanide to yield methylenecyclohexane, 1-methylcyclohexene and cycloheptene (equation 39)[77].



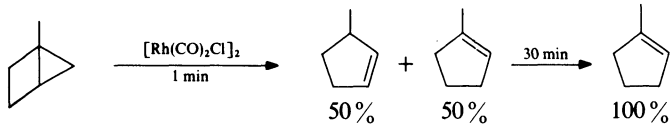
(**58**) (39)

With $[Rh(CO)_2Cl]_2$ bicyclo[4.1.0]heptane follows also the main pattern of less substituted bond fission to give a product (**59**), which then undergoes reduction with sodium borohydride in ethanol to lead to 1-hydroxymethyl-2-methylcyclohexane (**60**) (equation 40)[78].



(**58**) (**59**) (**60**) (40)

1-Methylbicyclo[2.1.0]pentane (**61**) was shown to rearrange to 1-methylcyclopentene when treated with $[Rh(CO)_2Cl]_2$ (equation 41). In fact, while Rh(I) is an excellent catalyst at room temperature, soluble Ag(I) complexes fail as catalysts at 100°C[79].

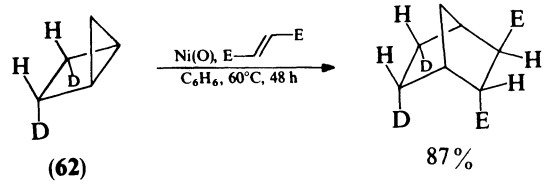


(**61**) (41)

Bicyclo[2.1.0]pentane (**62**) reacts thermally (120°C, 48 h), with electron-poor olefins via a stepwise, diradical mechanism to afford bicyclo[2.2.1]heptane products derived from the addition of the olefins on the *endo* side of the bicyclo envelope[80]. On the other hand in the presence of nickel(O) catalysts, the addition occurs under milder reaction conditions and with an alternative stereochemistry, i.e. predominantly on the *exo* face (equation 42)[81].

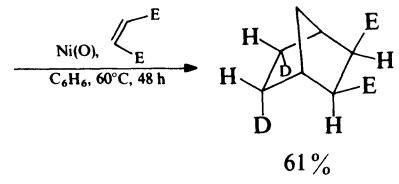
No class of transition metal catalysed rearrangements has been the subject of more controversy than those of bicyclobutane. A general mechanistic picture, consistent with the experimental facts, has, however, been presented[73a].

In analogy to 1,3-dienes, vinylcyclopropanes (**63**) provide a ligand of four π electrons for metal coordination with zerovalent transition metals such as $Fe(CO)_5$ (equation 43)[82a].

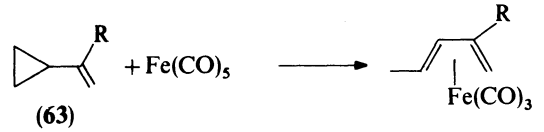


(62)

E = CO_2Me

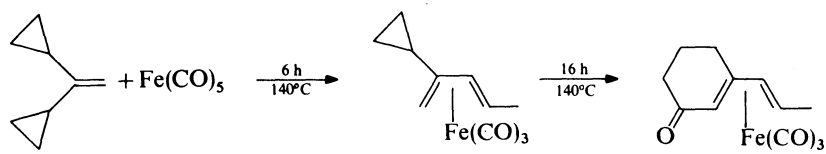


(42)



(63) (43)

When a mixture of equimolar quantities of 1,1-dicyclopropylethylene (**64**) and iron pentacarbonyl is heated at 140 °C for 6 h, 2-cyclopropylpenta-1,3-diene iron tricarbonyl (**65**) was obtained. On heating for 16 h 3-(1′-propenyl)-cyclohex-2-enone iron tricarbonyl (**66**), a ring-enlargement product resulting from a carbon monoxide insertion reaction coupled with a double cyclopropane ring-opening, was formed (equation 44)[82b].

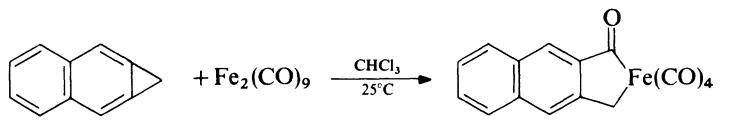


(44)

(64) (65) (66)

Other different modes of metal-mediated reactions of vinylcyclopropanes depending on substrate and reaction parameters have been reported[73b].

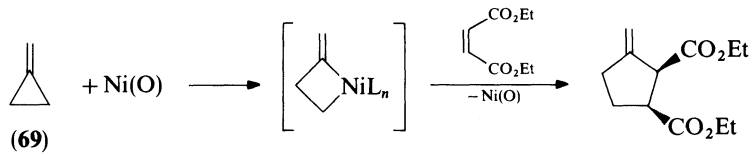
The reaction of naphtho[b]cyclopropene (**67**) with $Fe_2(CO)_9$ in chloroform at 25 °C yields a yellow crystalline $(C_{12}H_8O)Fe(CO)_4$ product (**68**) in 27% yield, resulting from the addition of an Fe–C bond of $Fe(CO)_5$ across one edge of the three-membered ring (equation 45)[82c].



(45)

(67) (68)

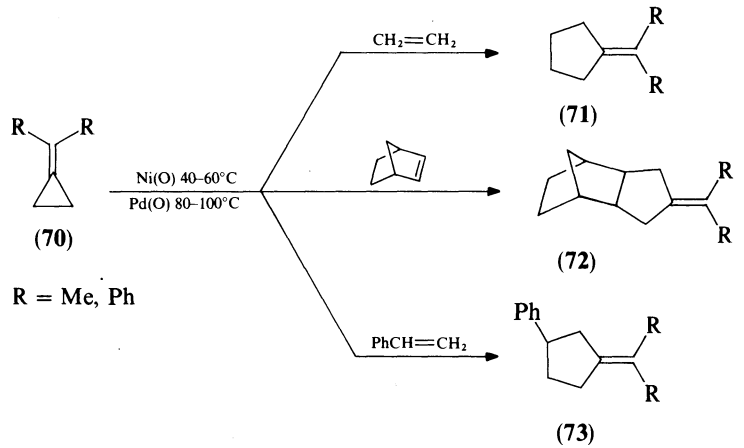
Methylenecyclopropane (**69**) has been shown to rearrange in the presence of Ni(O) to butadiene. When olefinic ligands are present in solution, the intermediate is trapped in a cycloaddition reaction (equation 46)[83].



(69) (46)

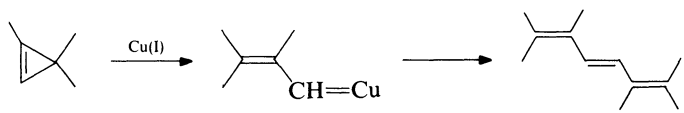
It may be assumed that Ni(O) first coordinates to the olefin before inserting into the σ bond. Effectively, the rearrangement to butadiene has been shown to proceed through a metal–olefin complex[83a].

Contrary to the parent compound, double bond disubstituted methylenecyclopropanes (**70**) react with Ni(O) or Pd(O) catalysts by cleavage of the C(2)–C(3) bond. In the presence of olefins such as ethylene, styrene or norbornene a relatively mild cyclodimerization into methylenecyclopentanes (**71–73**) is achieved in 75% or better yields (equation 47)[83c].



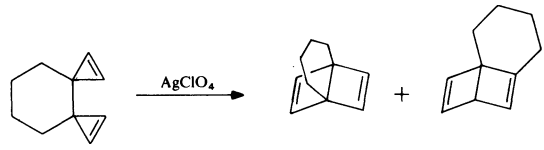
(47)

A metal-complexed carbene (**75**) was postulated as an intermediate in order to account for the unexpected formation of octatriene derivatives (**76**) in the copper(I)-catalysed dimerization of tri- and tetramethylcyclopropene (**74**) (equation 48)[84].



(74) (75) (76) (48)

A similar metal-complexed carbene was also involved for the isomerization and cleavage of a series of cyclopropenes in the presence of Ag(I)[85] and of thallic and mercuric acetates[86]. A series of Ag(I)-catalysed isomerizations of bicyclopropenyl compounds has been investigated [87, 88]. For instance, on treatment with $AgClO_4$ in different solvents at $-20\,°C$, 1,1′-tetramethylenebicyclopropenyl (**77**) yielded two Dewar benzenes (**78** and **79**) (equation 49)[88].

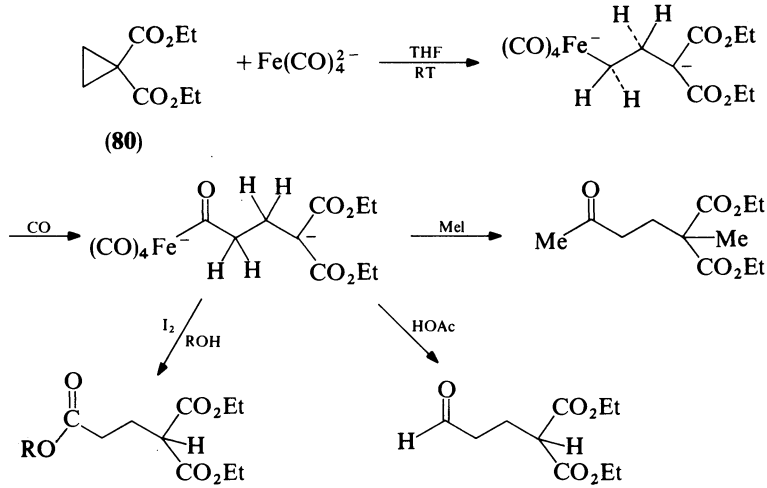


(49)

(77) (78) (79)

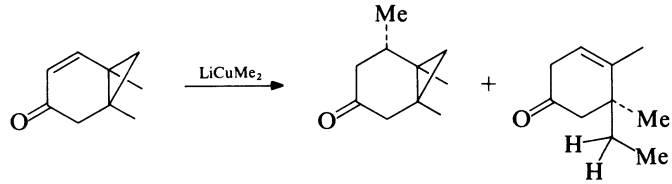
Interestingly, the percentage of the propelladiene (**78**) increased with increasing polarity of the solvent[88].

In sharp contrast to the extensive study devoted to electrophilic ring-openings[73], few investigations of cyclopropane ring-openings promoted by transition metal nucleophiles have been reported. It has been shown, however, that $Na_2Fe(CO)_4$–3/2 dioxane is an effective reagent for the nucleophilic ring-opening of diethyl 1,1-cyclopropanedicarboxylate (**80**) under CO at room temperature to produce a variety of carbonylated products (equation 50)[89].



(50)

The reaction of $LiCuMe_2$ with β-cyclopropyl α,β-unsaturated ketones (**81**) gave a 48 : 52 mixture of the normal conjugate addition product (**82**) and of the cyclopropane ring-opened product (**83**) (equation 51)[90].

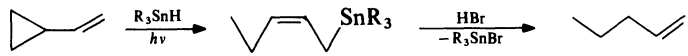


(51)

(81) (82) (83)

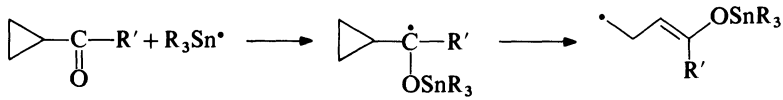
The high stereospecificity of the ring-opening reaction provides evidence against radical anion intermediates and is interpreted in terms of a direct nucleophilic attack of cuprate at the cyclopropyl carbon atom[90].

Selective reduction of the ring in vinylcyclopropanes is difficult to realize without reduction or displacement of the ethylenic bond. However, it has been shown that radical addition of an organotin hydride under UV irradiation, followed by protolysis of the adduct allows the specific reductive ring-opening of vinylcyclopropanes (equation 52)[91].



(52)

The mechanism probably involves radical attack as observed with the cyclopropyl ketones, via formation and opening of an intermediate cyclopropylcarbinyl radical into a homoallylic radical (equation 53)[92].



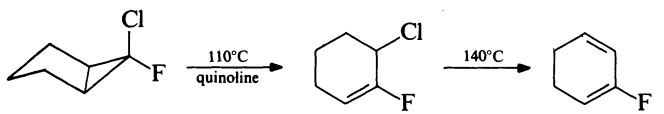
(53)

It has also been shown that preferential formation of primary alkyl radicals occurs in the ring-opening of ring-substituted cyclopropyl(stannyloxy)methyl and cyclopropyl(hydroxy) methyl radicals[93].

For other examples of four- and five-membered metallocyclic complexes, see Sections III.I and IV.A.3.

H. Halo- and Siloxycyclopropanes

The thermal or chemically induced ring-opening of gem-dihalocyclopropanes, readily available from the addition of dihalocarbene to olefins, has been widely studied[94]. The reaction is dependent not only on the kind of halogen but also on the molecular geometry of the substrate[95]. For instance, when *endo*-6-chloro-*exo*-6-fluorobicyclo[3.1.0]hexane (**84**) is treated with quinoline at 110°C and 140°C, 3-chloro-2-fluorocyclohexene (**85**) and 2-fluoro-1,3-cyclohexadiene (**86**) are obtained, respectively (equation 54)[95].

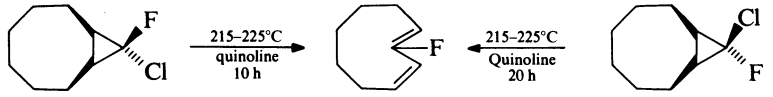


(54)

(**84**) (**85**) (**86**)

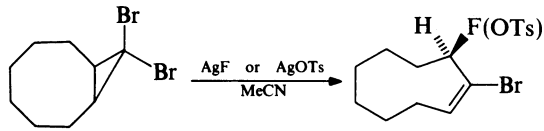
Under these conditions, the *exo*-chloro-*endo*-fluoro isomer was completely recovered. This stereospecificity, i.e. the strong dependence of the reaction rate upon the molecular geometry of the substrate, is reasonably explained by assuming that the rate-determining step of the ring-opening of gem-chlorofluorocyclopropanes is a concerted disrotatory process[4] in which the chlorine is removed in preference to the fluorine, to form the corresponding 2-fluoroallyl cation.

This specificity can be inverted in the case of the ring expansion of 9-chloro-9-fluorobicyclo[6.1.0]nonane; thus, due to the relative stability of the strained transition state, the ring expansion of the *exo*-chloro isomer (**87**) occurs faster than that of the *endo*-chloro isomer (**88**) (equation 55)[95].



(87) (88) (55)

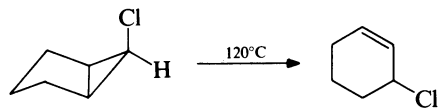
Stereospecific generation of halogenated and tosylated medium size rings (**90**) by ring-opening of gem-dibromocyclopropanes (**89**) was observed on heating with silver fluoride and tosylate in refluxing acetonitrile, respectively (equation 56)[96].



(89) (90) (56)

Examination of the reaction products revealed that one single diastereoisomer had been formed.

In the case of monohalocyclopropane derivatives, the reaction pathway also depends on the stereochemistry. Thus, *endo*-6-chlorobicyclo[3.1.0]hexane (**91**) is converted into 3-chlorocyclohexene (**92**) when heated at 120 °C for 4 h, whereas its *exo* isomer remains unchanged after heating at 250 °C for 4 h (equation 57)[97].



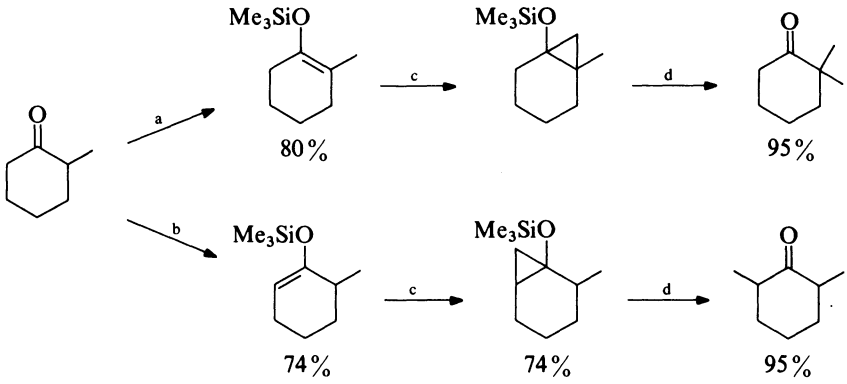
(91) (92) (57)

In the same way, the *endo*-chloro isomer of 3-chloro-8-oxatricyclo[3.2.1.$0^{2,4}$]octane undergoes ring expansion at 80 °C, while the *exo*-chloro isomer remains unchanged after being heated at 150 °C in nitrobenzene for 15 h[98].

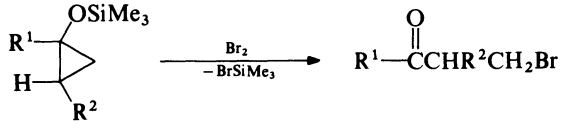
Trimethylsiloxycyclopropanes, readily available from silyl enol ethers and carbene or carbenoid species, constitute, now, very useful synthetic intermediates[99]. Thus, they undergo acid-, base-induced[100,101] or thermal[102] ring-opening into α-methylated aldehydes and ketones in very good yields. The reaction is highly regiospecific; in the case of an unsymmetrical ketone, monomethylation can be oriented either to the α- or α′-position (equation 58)[100]. This sequence has been applied to ethylenic ketones and in the steroid field[103].

The bromination of siloxycyclopropanes (**93**) gives the derived α-bromomethyl aldehydes or ketones (**94**) (equation 59)[104].

Siloxycyclopropanes are quantitatively converted into β-acetoxymercuriketones by reaction with mercuric acetate. Successive treatment with $PdCl_2$ or $PdCl_2 + CO$ gives α-methyleneketones or γ-ketoesters, respectively. The ring cleavage takes place highly selectively at the least substituted cyclopropane carbon atom (equation 60)[105].

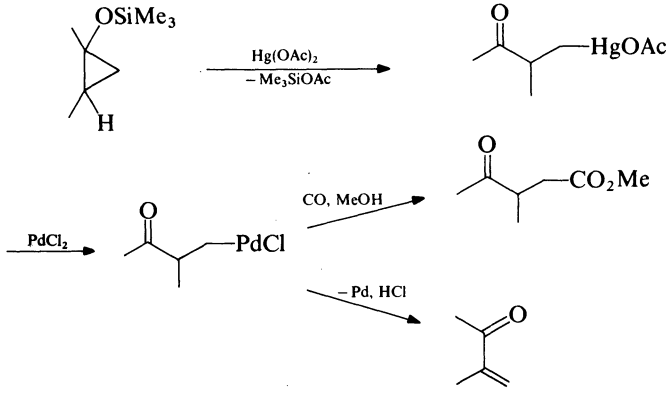


(a) NEt_3, $ClSiMe_3$, DMF; (b) $LiN(Pr\text{-}i)_2$, $ClSiMe_3$;
(c) Zn–Ag, CH_2I_2, pyridine; (d) MeOH, H_2O, 1% NaOH, reflux. (58)



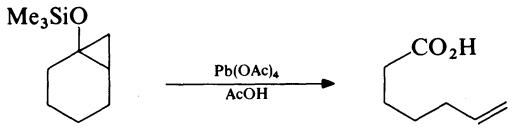
(59)

(93) **(94)**



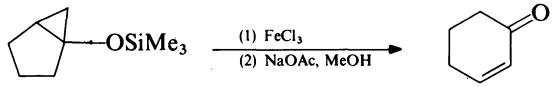
(60)

The treatment of siloxycyclopropanes with lead(IV) acetate in acetic acid leads to ω-unsaturated acids (equation 61)[106].



(61)

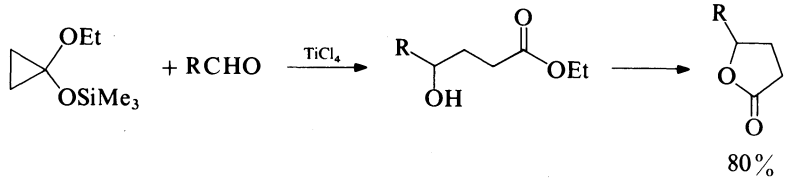
Upon treatment with ferric chloride, followed by treatment with sodium acetate in methanol, siloxycyclopropanes give 2-cycloalkenones in high yields (equation 62)[107].



(62)

Similar reactions with bis(trimethylsiloxy)bicyclo[4.1.0]alkanes afford cycloalkane-1,3 diones[107].

1-Ethoxy-1-trimethylsiloxycyclopropane (**95**) acts as a synthetic equivalent of the β-anion of ethyl propionate (see equation 14). It reacts with a wide range of saturated aliphatic and aromatic aldehydes in the presence of titanium(IV) chloride to produce γ-hydroxyesters (**96**), usually isolated as γ-lactone derivatives (**97**) (equation 63)[108].

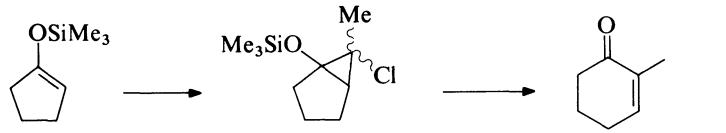


(63)

(**95**) (**96**) (**97**)

Ketones cannot be employed as such, but the corresponding acetals react satisfactorily. Other common Lewis acids (i.e. $Hg(OAc)_2$, $SnCl_4$, Bu_3SnOTs) besides $TiCl_4$ are totally ineffective or give different products.

Aldehydes and ketones are readily converted into higher α-halo-α-ethylenic homologues on addition of dihalocarbene CX_2 to enol ethers and acetates, to enamines and to trimethylsilyl enol ethers and subsequent opening of the cyclopropane ring[109]. The cycloaddition of chloromethylcarbene to cycloalkanone trimethylsilyl enol ethers (**98**) and elimination of $ClSiMe_3$ from the intermediate chlorosiloxymethylcyclopropanes (**99**) upon heating in toluene or in methanol containing triethylamine, produces homologous α-methylcycloalkenones (**100**) (equation 64)[109].

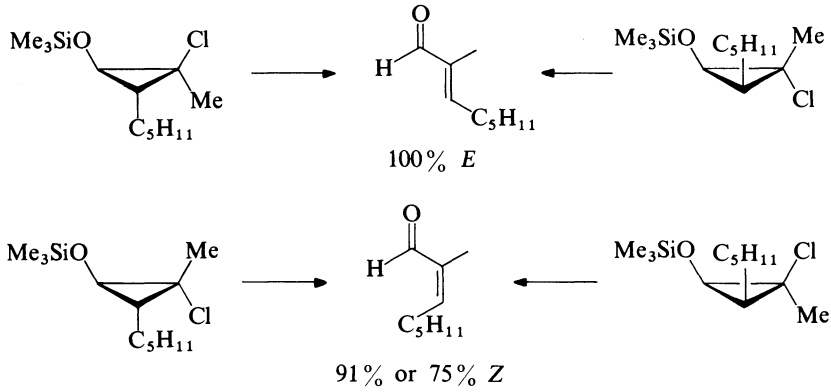


(64)

(**98**) (**99**) (**100**)

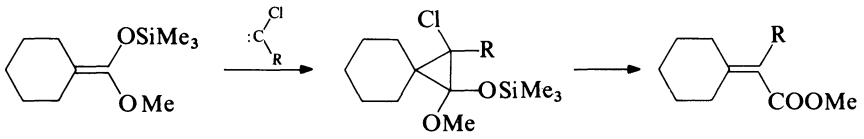
This sequence transforms acyclic ketones and aldehydes into α-methylene ketones and α-methyl-α,β-unsaturated ketones and aldehydes[110]. It has been illustrated by the synthesis of eucarvone, (±)-nuciferal and (±)-manicone[111]. This ring-opening of chlorosiloxycyclopropanes with $ClSiMe_3$ elimination appears to be a practical route to *Z* or *E* α,β-ethylenic aldehydes and ketones depending on the stereochemistry of the reactants. For example, conversion in MeOH–NEt_3 at 20°C of the 2-chloro-2-methyl-3-pentyl-1-trimethylsiloxycyclopropanes (derived from the addition of the chloromethylcarbene to the *E* and *Z* silyl enol ethers of *n*-heptanal) leads either to *E* or *Z* 2-methyl-oct-2-enal (equation 65)[112].

This rearrangement is also a remakable illustration of the Woodward–Hoffmann–DePuy rules concerning the disrotatory ring-opening of halocyclopropanes[5].



(65)

In a related reaction, addition of chloro-, chloromethyl-, chlorophenyl or chlorofluorocarbene to ketene alkylsilyl acetals and subsequent ring-opening (MeOH–NEt_3 reflux) leads to the corresponding 2-substituted-2-alkenoic esters in high yields (equation 66)[113].



R = H, Me, Ph, F

75–90%

(66)

III. $C_3 \rightarrow C_4$ RING ENLARGEMENTS

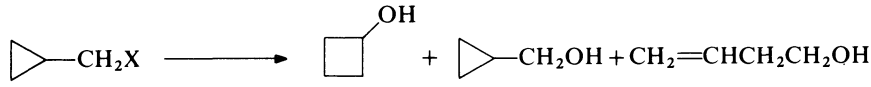
Cyclopropanes adjacent to an electron-deficient centre X (carbon or heteroatom) undergo $C_3 \rightarrow C_4$ ring enlargement into four-membered ring derivatives via routes involving cations, radicals or carbene intermediates. Furthermore, when the cyclopropanes also bear on the same carbon an electron-donor substituent Y they undergo a specific $C_3 \rightarrow C_4$ ring expansion, important from the synthetic point of view, into cyclobutanone (or related) derivatives (equation 67).

(67)

Y = O, S, N
X = C, C=C, C=O, N

A. Cyclopropylcarbenium Ion

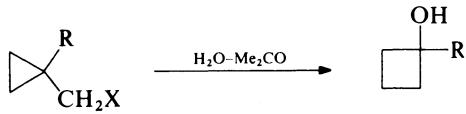
Cyclobutyl compounds are significant products of the $C_3 \rightarrow C_4$ ring enlargement of cyclopropylmethyl derivatives; thus, deamination of cyclopropylmethylamine[114], hydrolyis of the β-naphthalenesulphonate of cyclopropylmethanol[115] or treatment of cyclopropylmethanol itself with aqueous hydrochloric acid[114] lead to cyclobutanol in 40, 42 and 72% yields respectively, plus cyclopropylmethanol and 3-buten-1-ol (equation 68).



X = NH_2	40%	56%	4%
β-naphthalenesulphonate	42%	58%	trace
OH	72%	—	—

(68)

Exclusive formation of cyclobutyl products occurs in similar reactions of 1-methyl or 1-phenylcyclopropylmethyl systems (equation 69)[161, 117].

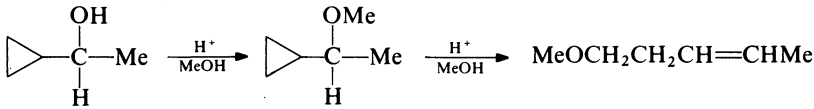


R = Me, Ph

90–100%

(69)

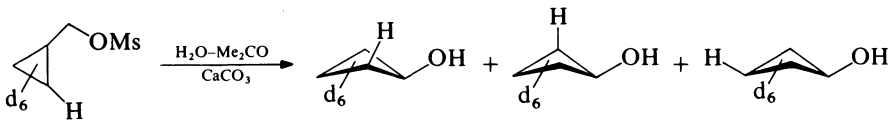
On the other hand, cyclobutyl compounds are not obtained from cyclopropylmethyl derivatives with carbenium ion stabilizing substituents on the carbinyl carbon. For example, reactions of methylcyclopropyl methanol (**101**) with acidic reagents led to unrearranged or on further heating to 3-penten-1-yl derivatives (equation 70)[118].



(**101**)

(70)

The cyclobutyl products from ring enlargement of cyclopropylmethyl derivatives are formed with high stereoselectivity. Thus, it has been shown that cyclopropylcarbinyl-1,1′,1′-*trans*-2,3,3-d_6 mesylate (**102**) containing only a single hydrogen atom as label, undergoes solvolysis in 60% aqueous acetone buffered by $CaCO_3$, to give cyclobutanols where in the 2, 3 and 4 positions the hydrogen was 91.3% *cis* to the hydroxyl (equation 71)[119].



(**102**)

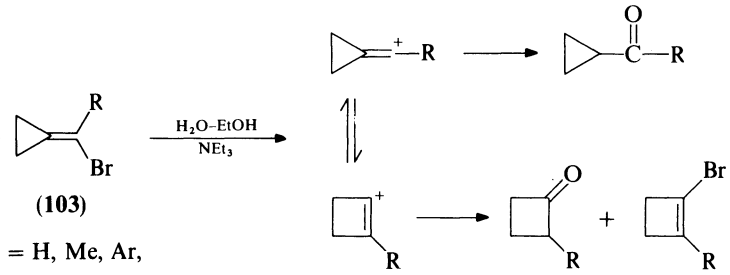
(71)

A bicyclobutonium ion, which is the resonance hybrid of a cyclopropylcarbinyl, a cyclobutyl and a homoallyl cation is considered to account for the reactivity of this system (equation 72)[120].

(72)

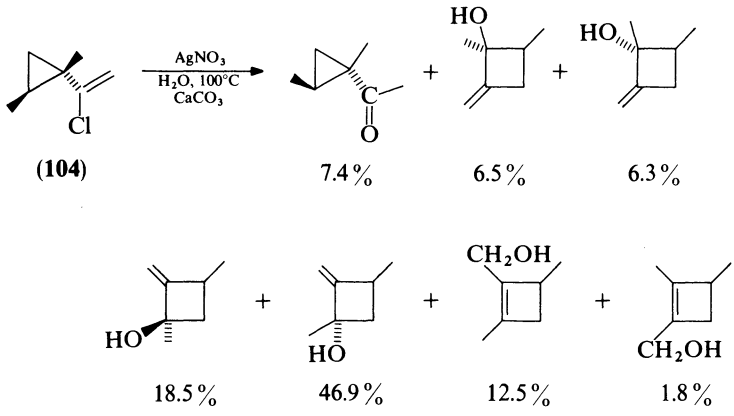
This ion has significant bonding between C(1) and C(4) and hence significant positive charge at C(2): it is assumed to be in rapid equilibrium with isomers in which C(1), C(3) and C(4) have interchanged positions[121]. Another proposal has been made by Brown, who suggests that the classical cyclobutyl cation is in rapid equilibrium with the cyclopropylcarbinyl cation and that both react with solvent to give products[122]. NMR data have clearly shown that the tertiary cyclopropylcarbinyl ions have an unrearranged structure[121].

In the same way, the cyclopropylidenemethyl cations produced on solvolysis of cyclopropylidenemethyl bromides (**103**) undergo $C_3 \rightarrow C_4$ ring enlargement into cyclobutanones depending upon the ability of the electron-releasing substituents in the α-position to stabilize the intermediate vinyl cations (equation 73)[123].



(73)

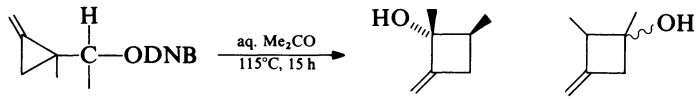
When R = H, the solvolysis in 50% aqueous methanol in the presence of 1.2 equivalent of trimethylamine gave exclusively cyclobutanone; when R = Me, solvolysis in 60% aqueous ethanol led to 2-methylcyclobutanone and 1-bromo-2-methylcyclobutene (from internal return) in 35 and 65% yields, respectively[123]. But when R = phenyl[123], *p*-tolyl[124], *p*-anisyl[124] or cyclopropyl[125], the corresponding cyclopropyl ketones are the main non-rearranged products (52–84%). Consequently, the higher the stability of the intermediate vinyl cation, the less the amount of product of $C_3 \rightarrow C_4$ ring enlargement is obtained[123]. Hydrolysis of *trans*-1,2-dimethylcyclopropylvinyl chloride (**104**) in the presence of silver nitrate occurs with $C_3 \rightarrow C_4$ ring enlargement into 2-methylenecyclobutanols in 92% yield (equation 74)[126].



(74)

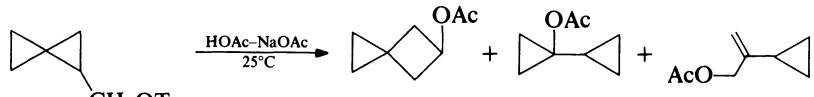
From the nature of these compounds it can be easily seen that in the ring expansion the most substituted bond of the cyclopropane ring is preferentially involved. In order to account for the stereoselectivity of the rearrangement, i.e. 68 % of the *cis* stereochemistry of the two methyl groups of the cyclopropylvinyl chloride (**104**) is retained in the methylenecyclobutanols, the intermediacy of a methylenebicyclobutonium cation was suggested[126].

Solvolysis of (1-methyl-2-methylenecyclopropyl)methylcarbinyl-3,5-dinitrobenzoates (**105**) in aqueous acetone in the presence of 2,6-lutidine led to $C_3 \rightarrow C_4$ ring enlargement products (equation 75)[127].



(**105**) 32.3 % 61.2 % (75)

Acetolysis of spiropentylcarbinyl tosylate (**106**) at room temperature gave 5-spirohexyl acetate (**107**) from $C_3 \rightarrow C_4$ ring expansion, 1-cyclopropylcyclopropyl acetate (**108**) from cyclopropylcarbinyl to cyclopropylcarbinyl cation rearrangement and 2-cyclopropylallyl acetate (**109**) from subsequent ring-opening of the rearranged cyclopropylcarbinyl cation (equation 76)[128].



(**106**) (**107**) (**108**) (**109**) (76)

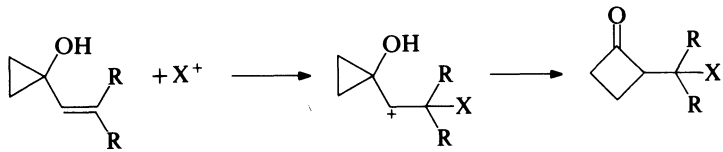
48 % 11 % 23 %

In accordance with the previous observations of Dauben[129] and Schleyer[119] the cyclopropylcarbinyl–cyclobutyl cation rearrangement proceeds with net inversion at the migration origin upon nucleophilic attack.

B. 1-Vinylcyclopropanol

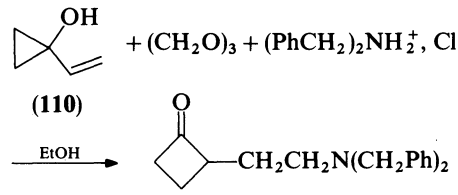
1-Vinylcyclopropanols can be prepared either from the readily available cyclopropanone hemiacetal[32], from 1-hydroxycyclopropanecarboxaldehyde derivatives[131], from α,α′-dichloroacetone[132], from the silver Simmons–Smith cyclopropanation of α-ethylenic ketone silyl enol ethers[99a,b], from the dye-sensitized photo-oxygenation of alkylidenecyclopropanes[99c] or from the ring-opening of oxaspiropentanes (cf. Section III.C). Consequently, they become participants of choice in a number of useful chemical transformations (see also Section IV.A).

Effectively, they undergo ring expansion into cyclobutanones with a variety of electrophilic reagents; with hydrobromic, perbenzoic acids and with *tert*-butyl hypochlorite, 2-alkyl-, 2-hydroxymethyl- and 2-chloroalkylcyclobutanones are obtained, respectively[130]. The rearrangement takes place most probably through an intermediate cyclopropylcarbinyl cation (equation 77).



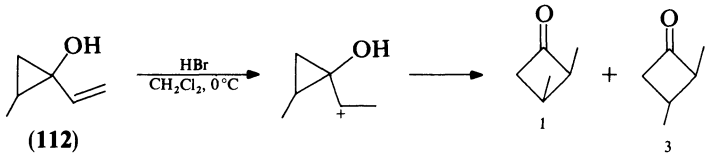
X = H, OH, Cl (77)

With trioxymethylene and dibenzylamine hydrochloride in refluxing ethanol 1-vinylcyclopropanol (**110**) undergoes a Mannich-type reaction to yield the corresponding 2-(2-dibenzylamino)ethylcyclobutanone (**111**) (equation 78)[130].

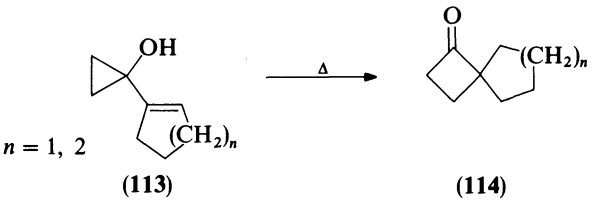


(78)

When 2-methyl-1-vinylcyclopropanol (**112**) is treated with dry hydrogen bromide in methylene chloride at 0°C for 5 min a mixture of *cis*- and *trans*-2,3,-dimethylcyclobutanones is formed in a 1:3 ratio (equation 79)[130]. This result is consistent with the preferred migration of the more highly substituted carbon atom, recently observed in the peracid oxidation of methylenecyclopropanes (*vide infra*)[133]. On simple heating at 100°C in the liquid phase 1-cyclopentenyl and 1-cyclohexenylcyclopropanols (**113**) are quantitatively converted into the corresponding spiroketones (**114**) (equation 80)[132].

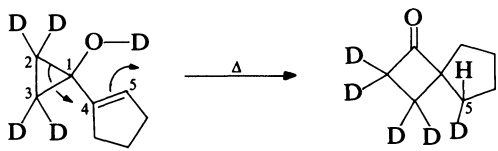


(79)



(80)

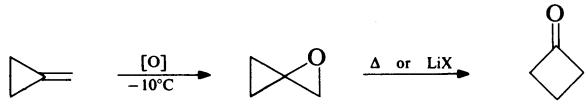
The stereochemistry and mechanism of such a thermal ring enlargement have been determined by the examination of the product of rearrangement of a perdeuteriocyclopropanol. Although thermally allowed, a concerted process[5] is ruled out by the occurrence of an *anti* configuration for the deuterium atom on C(5) of the spiroketone, implying an intramolecular stereospecific *syn* addition of the deuterium from the O–D and of the cyclopropane bond (C(2)–C(4) bonding) on the double bond (equation 81)[132].



(81)

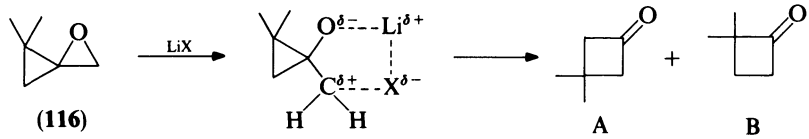
C. Oxaspiropentane

The intermediacy of oxaspiropentanes was first proposed in some reactions: *i.e.* the addition of diazomethane to cyclohexanone[134], the reaction of dimethyloxosulphonium methylide with α-haloketones[135] and the reaction of *N,N*-dimethylaminophenyloxosulphonium cyclopropylide with ketones[136]. The parent oxaspiropentane (**115**) has been obtained from the *p*-nitroperbenzoic acid oxidation of a methylene chloride solution of methylenecyclopropane (**69**) at −10°C (equation 82)[137].



(**69**) (**115**) (82)

On heating, liquid oxaspiropentane at 100°C undergoes isomerization into 2-methylacroleine (30%), methyl vinyl ketone (30%) and cyclobutanone (40%). Flow pyrolysis in the injector (230°C) of a gas chromatograph (col. 100°C) increases the yield of cyclobutanone to 80%. The effect of Lewis acid on epoxide rearrangements is well known in the field of small ring compounds[138]; indeed, addition of a catalytic amount of lithium iodide results in an exothermic conversion of oxaspiropentane into cyclobutanone in 95% yield, thus providing a convenient and rapid route to cyclobutanone from commercially available cheap reagents[139]. The epoxide prepared from 2,2-dimethylmethylenecyclopropane (**116**) rearranges with Lewis acids to form 3,3-dimethyl- and 2,2-dimethylcyclobutanones A and B (equation 83)[140].

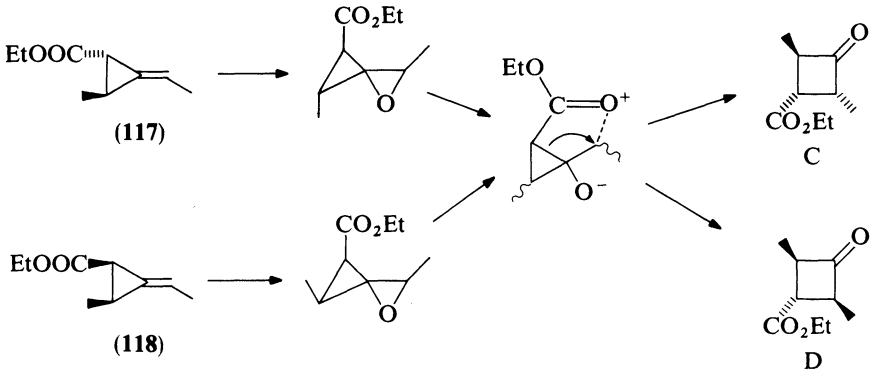


(**116**) (83)

The dependence of the product ratio on the nature of the catalyst (A/B = 7.5, 10 and 15 with lithium iodide, perchlorate and tosylate, respectively) provides strong evidence for a mechanism involving nucleophilic ring-opening to lithio–halohydrin-type intermediates[132]. The amount by which tertiary migration is favoured over primary migration may depend on the degree of positive charge development at the migrating centre in the rearrangement. In contrast, the addition of diazomethane to dimethylketene leads to a 2:1 mixture of ketones A and B[141]. On the other hand, the stereochemistry is lost in the peracid oxidation of the *trans*- and *cis*-2-methyl-3-ethylidene-1-ethoxycarbonylcyclopropanes (**117** and **118**), both of which yield the same mixture of cyclobutanones C and D (ratio 72:28) suggesting a common intermediate (equation 84)[133].

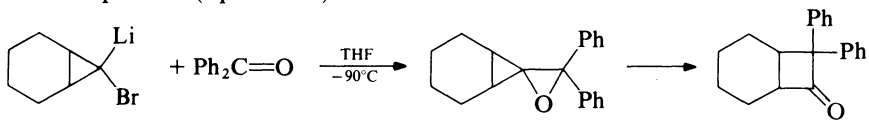
The most curious feature of these reactions is that the observed products can only be rationalized by preferential migration of the ester-bearing carbon to the electron-deficient centre of a cyclopropylcarbinyl cation. This is not at all the expected substituent effect for such an electron-withdrawing group.

While α',α'-diphenylmethylenecyclopropane undergoes ring enlargement into 2,2-diphenylcyclobutanone upon treatment with selenious acid[142], reaction of methylenecyclopropane with thallium(III) nitrate or mercury(II) hypochlorite leads mainly to ring fission products besides a low percentage (18%) of cyclobutanone[143]. In addition to their formation by epoxidation of cyclopropylidene compounds, oxaspiropentanes are



(84)

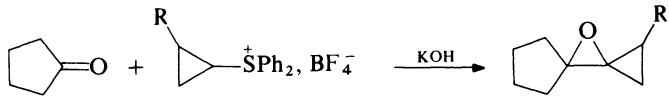
available through the nucleophilic addition of 1-lithio-1-bromocyclopropanes to ketones at low temperature (equation 85)[144].



85% (85)

They can be isolated when working up under basic conditions but they undergo readily the $C_3 \rightarrow C_4$ ring expansion into cyclobutanones under acidic conditions.

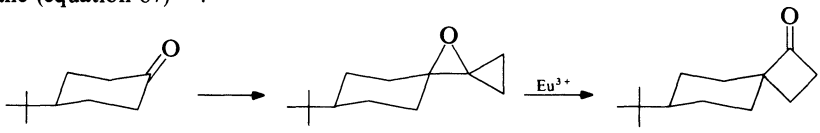
Oxaspiropentanes have been also obtained in 59–100% yields from the condensation of aldehydes and ketones with the diphenylsulphonium cyclopropylide prepared by treatment of the cyclopropyldiphenylsulphonium fluoroborate (**119**) with solid potassium hydroxide in dimethyl sulphoxide at 25°C (equation 86)[145].



(86)

R = H, Me (**119**)

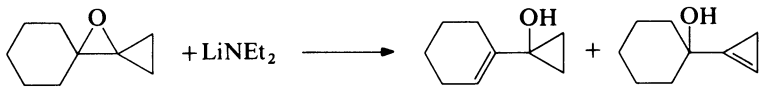
Similarly 2-methylcyclopropyldiphenyl sulphonium fluoroborate gives methyl-substituted oxaspiropentanes. Whereas dialkyl and arylalkyl ketones allow easy isolation of these reactive compounds in neutral or basic conditions, the oxaspiropentanes from benzophenone and cyclopropyl methyl ketone are not isolable but rearrange to the corresponding cyclobutanones. The lability of the oxaspiropentanes toward ring expansion is a consequence of the high stability of the cation formed by heterolysis of the carbon–oxygen bond. The reaction proceeds with very high stereoselectivity in most cases, addition of the ylide to 4-*t*-butylcyclohexanone results in a single isomer of oxaspiropentane (equation 87)[145].



(87)

The fact that equatorial attack occurs exclusively, is deduced by consideration of the stereospecific ring enlargement into a single cyclobutanone: *inversion* at the migration terminus is obtained upon treatment with europium(III)[145].

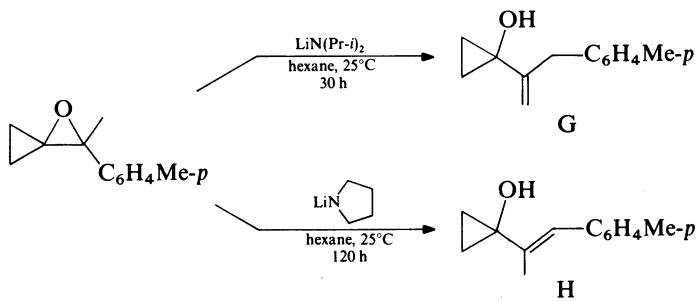
The ring-opening of oxaspiropentanes induced by lithium dialkylamide, such as lithium diethylamide, leads to the allyl alcohols E and F in ratios highly depending on the nature of the solvent (e.g., the E/F ratio is 1.5 and 9 in ether and pentane, respectively) (equation 88).



	E	F
ether	1.5	1
pentane	9	1

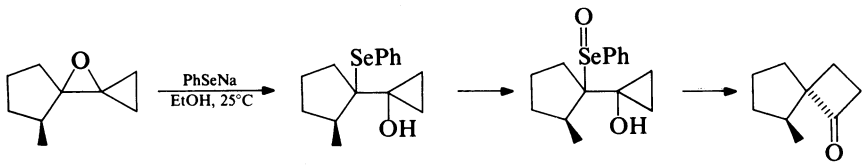
(88)

The regioselectivity in the base-induced ring-opening can also be determined by kinetic or thermodynamic control of the reaction (equation 89)[146].



(89)

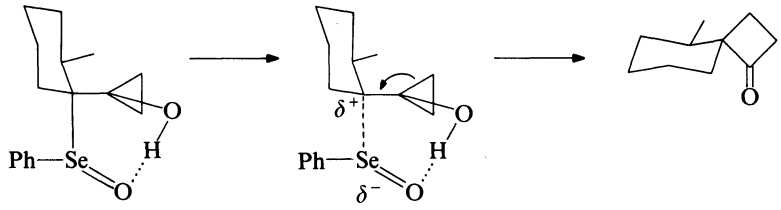
Thus, the use of a sterically hindered base for relatively short time in an hydrocarbon solvent shows a kinetic preference for the abstraction of a proton from the methyl group leading to vinylcyclopropanol G; the use of a sterically less demanding base for longer times in a hydrocarbon solvent provides the thermodynamically more stable vinylcyclopropanol H (98% *trans*)[146]. Oxaspiropentanes undergo smooth opening with sodium phenylselenide in ethanol to give β-hydroxyselenides at room temperature. Then, oxidation with *m*-chloroperbenzoic acid at -78 to $-30\,^{\circ}C$ and ring enlargement at $-30\,^{\circ}C$ in the presence of pyridine lead directly to cyclobutanones (equation 90)[147].



(90)

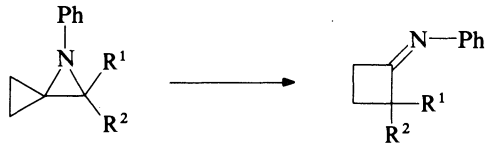
The addition of phenylselenide to oxaspiropentanes is highly accelerated by protic solvents which protonate and weaken the C–O bond, thus increasing its tendency toward nucleophilic attack. Furthermore, the epoxide opening by selenide is stereospecific and the stereochemistry obtained is opposite to that normally produced by the acid-catalysed rearrangement of oxaspiropentane (see equation 87). The selenoxide seems to play the role

of a leaving group and the intermediate would be expected to prefer a conformation in which the selenoxide is hydrogen bonded to the hydroxyl group. This conformation perfectly lines up one of the cyclopropane bonds for axial back-side migration once the selenoxide leaves (equation 91)[147].



(91)

Azaspiropentanes (**120**) react in the same manner as oxaspiropentanes (equation 92).

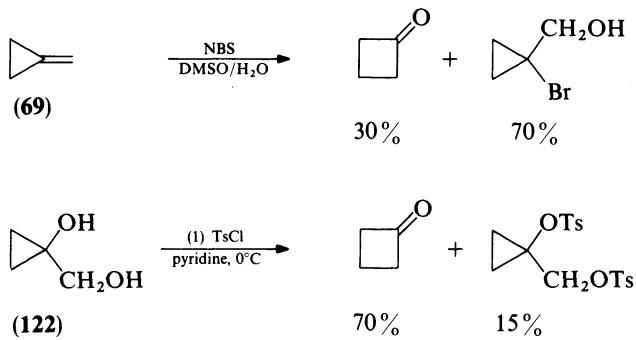


(92)

(**120**) (**121**)

Prepared at −78 °C the triphenyl compound ($R^1 = R^2 = Ph$) gives the corresponding cyclobutanimine (**121**) on warming to room temperature. The diphenyl compound ($R^1 = H$, $R^2 = Ph$) can be rearranged either on heating to 100 °C or by treatment with hydrogen chloride in benzene, or by prolonged irradiation in methylene chloride[148]. On the other hand, the monophenyl derivative ($R^1 = R^2 = H$) gives only ring-opening products on treatment with hydrogen chloride, though its rearrangement can be effected either by prolonged irradiation in benzene or by gas phase thermolysis[148,149].

Rearrangements related to the $C_3 \rightarrow C_4$ ring expansion of oxaspiropentanes occur on treating methylenecyclopropane (**69**) with *N*-bromosuccinimide (NBS) and water in DMSO or on reaction of 1-hydroxycyclopropylmethanol (**122**) with *p*-toluenesulphonyl chloride in pyridine (equation 93)[132].



(93)

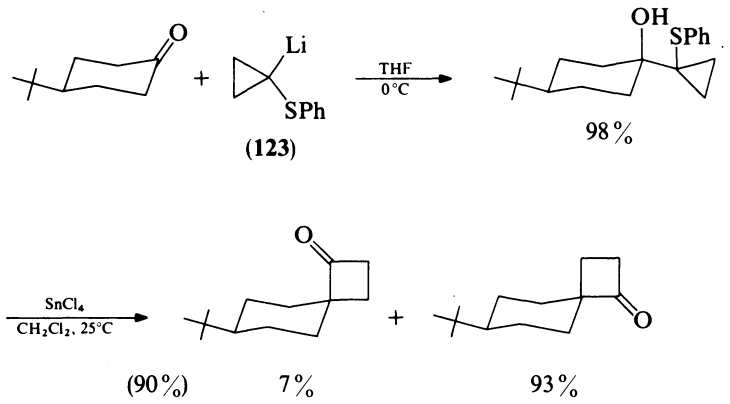
(**69**) 30% 70%

(**122**) 70% 15%

Methylenecyclopropane (**69**) probably first yields a mixture of the two α-bromo alcohols, the cyclopropanol subsequently rearranging to cyclobutanone. In the case of the diol (**122**), the initially formed primary tosylate may undergo either ring expansion or a second tosylation. Replacement of pyridine by the more basic and less nucleophilic 2,6-lutidine increases the yield of cyclobutanone to 80%. It must be emphasized that the 1-hydroxycyclopropyl methanol (**122**) itself undergoes ring expansion into cyclobutanone (60%) upon treatment with a trace of $BF_3.Et_2O$[132]; such a rearrangement has been used in the conversion of phorbol to phorbobutanone[150]. For other examples of related acid-catalysed ring enlargement see Section III.E.

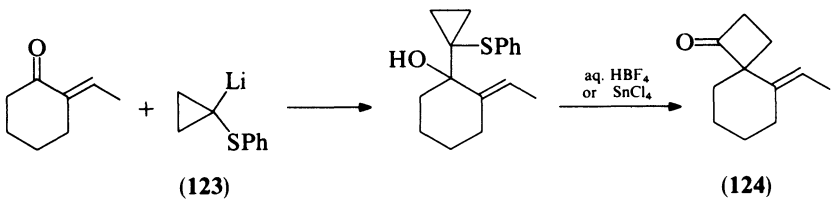
D. Sulphide-, Selenide- and Methoxycyclopropyl Derivatives

Reaction of 1-lithiocyclopropyl phenyl sulphide (**123**) with 4-*t*-butylcyclohexanone produces an adduct as a 99:1 mixture of two isomers. By analogy to organometallic addition to this ketone, the stereochemistry is assumed to result from equatorial attack. Treatment of the adduct with one equivalent of anhydrous stannic chloride followed by hydrolysis produces primarily cyclobutanones (equation 94)[151].



(94)

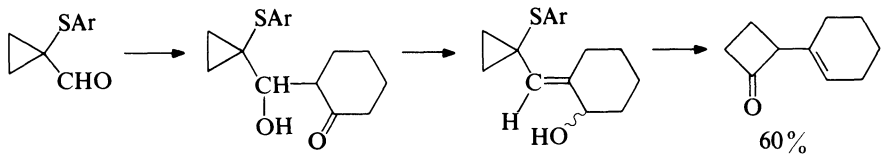
Formation of the product requiring *retention* of configuration at the migration terminus strongly suggests a carbenium ion intermediate rather than a migration concerted with loss of the leaving group. Similar results have been obtained by utilizing 2,6-dimethyl-2-cyclohexen-1-one (cf. equation 87). To test whether conformational or electronic effects account for the high stereoselectivity of the reaction, the spiroannelation of 2-ethylidene-cyclohexanone was performed. Upon treatment with aqueous fluoroboric acid or stannic chloride a single cyclobutanone (**124**) was obtained in 39 and 84% yields, respectively (equation 95)[151].



(123) (124)

(95)

Orbital symmetry demands that the formation of this cyclobutanone (**124**), occurs with retention of configuration of the migrating carbon in a suprafacial two-electron [1, 2] shift[151]. The use of this sulphide allows one to overcome the limitations of the method based on the phenylsulphonium cyclopropylide: i.e., the preferred conjugate addition with formation of spiropentanes instead of carbonyl addition with α,β-unsaturated carbonyls and the sluggishness of reaction with hindered ketones[152]. Quenching 1-lithiocyclopropylphenyl sulphide (**123**) with dimethyl formamide gives 1-phenylthiocyclopropanecarboxaldehyde (**125**) which is able to undergo aldol condensation with ketone enolates to provide, after dehydration and reduction, allylic alcohols (**126**) vinylogous of the cyclopropylcarbinol obtained in equation 95. Then, upon addition to a mixture of 48% fluoroboric acid and ether they undergo $C_3 \rightarrow C_4$ ring expansion into 2-vinylcyclobutanones (**127**), in moderate yields (equation 96).

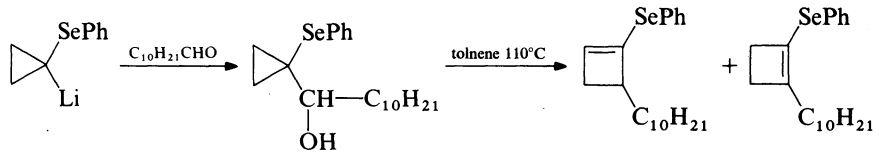


(**125**) (**126**) (**127**)

(96)

The use of 2,6-dimethoxyphenyl as the aryl group of the cyclopropyl sulphide provides electronic acceleration for the migration of the cyclopropyl bond and steric bulk which reduces the nucleophilicity of the thiol. Consequently, the cleanliness and the yield of the reaction are improved[153].

1-Lithio-1-cyclopropyl selenides (**128**) react with aldehydes and ketones to give β-hydroxycyclopropyl selenides (**129**) which undergo dehydration and $C_3 \rightarrow C_4$ ring expansion upon treatment with (carboxysulphamoyl)triethylammonium hydroxide inner salt methyl ester ($MeO_2CH^-SO_2N^+Et_3$) (equation 97)[154].

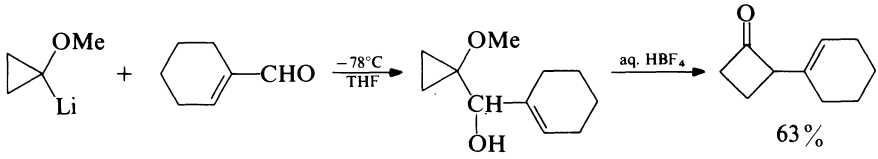


(**128**) (**129**) 60% (15:85)

(97)

The same reaction with methyl *p*-tolyl ketone gave a β-hydroxycyclopropyl selenide which upon treatment with *p*-toluenesulphonic acid underwent ring expansion to 2-methyl-2-*p*-tolylcyclobutanone, a precursor of α-cuparenone[155].

1-Methoxycyclopropyllithium (**130**) prepared by reductive lithiation of 1-phenylthio-1-methoxycyclopropane by two equivalents of lithium 1-(dimethylamino)naphthalenide[156a] or from 1-bromo-1-ethoxycyclopropane[156, b,c] reacts with conjugated aldehydes and ketones at −78°C in THF to yield 1-cyclopropylallyl alcohols (**131**) by specific 1,2-addition. Then, upon treatment with 10% aqueous HBF_4 they undergo the known $C_3 \rightarrow C_4$ ring enlargement of α-substituted cyclopropyl ethers[157] into 2-phenyl or 2-vinylcyclobutanones, in satisfactory yields (equation 98)[156].



(130) (131)

(98)

These 2-vinylcyclobutanones are unusually promising intermediates for the versatile elaboration of five-[158,159], six-[158,160] and eight-membered rings[161]. They also undergo the photochemical oxa-di-π-methane rearrangement[162].

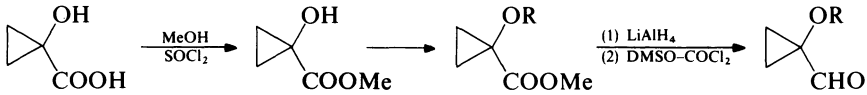
E. 1-Hydroxycyclopropylcarbonyl Compounds and Derivatives

Attempts to prepare 1-hydroxycyclopropanecarboxaldehyde (**132**) have failed; it undergoes spontaneous $C_3 \rightarrow C_4$ ring enlargement into 1-hydroxycyclobutanone (**133**) (equation 99)[132].

(132) (133)

(99)

Moreover, contrary to other cyclobutanols bearing an adjacent potential electron-deficient centre (*vide infra*, Section V.B) the 1-hydroxycyclobutanones do not apparently undergo $C_4 \rightarrow C_3$ ring contraction into 1-hydroxycyclopropanecarboxaldehyde derivatives[163,164]. In fact, the pattern of labelling in D_2O–NaOD suggests an equilibrium between the two isomeric acyloins in favour of the four-membered ring[165]. However, when the hydroxyl group is protected (i.e. methoxyethoxymethyl or tetrahydropyranyl ethers, or as trimethylsiloxy or *t*-butyldimethylsiloxy ethers[131,166]) the 1-hydroxycyclopropanecarboxaldehyde derivatives (**135**) are sufficiently stable to be prepared and handled. They have been obtained in high yields from the readily available 1-hydroxycyclopropanecarboxylic acid (**134**)[167] upon successive esterification (MeOH, $SOCl_2$)[131], *O*-silylation[168,169] or hydroxyl protection[131,166], reduction with $LiAlH_4$ or DIBAH and oxidation with oxalyl chloride activated dimethyl sulphoxide[170] (equation 100)[131].



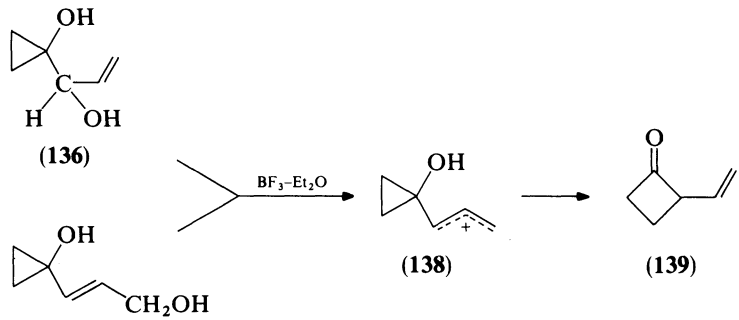
(134) (135)

R = $MeOCH_2CH_2OCH_2$, Me_3Si, *t*-$BuSiMe_2$

(100)

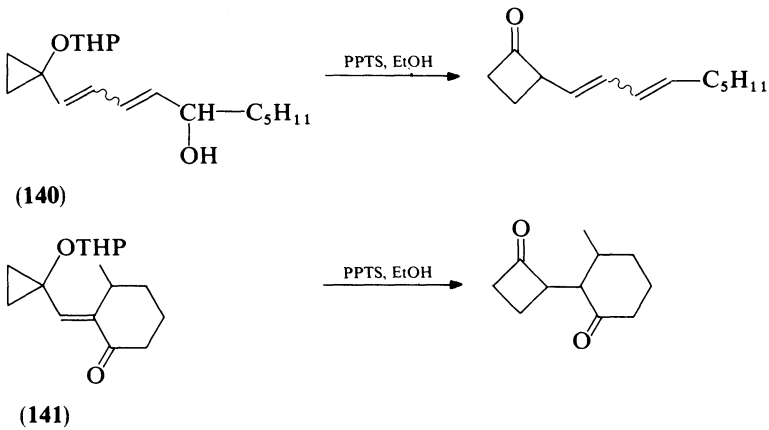
The aldehyde derivative (R = EtOCH(Me)-) has been prepared from the cyclopropanone cyanohydrin[171]. The 1-(1-hydroxycyclopropyl)- and 3-(1-hydroxycyclopropyl)

propenols (**136** and **137**) have been obtained from the 1-hydroxycyclopropanecarboxaldehyde tetrahydropyranyl ether (**135**) in 78 and 80% yields, respectively. Both vinylogous diols undergo a complete $C_3 \rightarrow C_4$ ring enlargement to 2-vinylcyclobutanone (**139**)[172] upon simple addition of a catalytic amount of boron trifluoride etherate at room temperature (equation 101)[131].



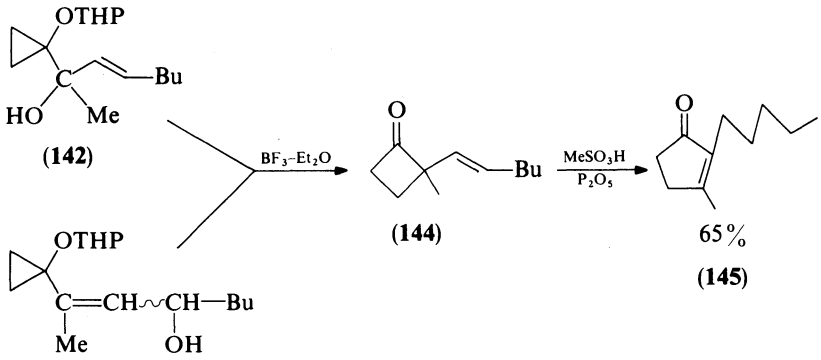
(101)

The rearrangement which involves the intermediacy of the same cyclopropylcarbinyl cation (**138**) is completed in few minutes as monitored by t.l.c. Upon treatment with 10 mol% of pyridinium *p*-toluenesulphonate (PPTS)[173] in ethanol at 55°C in order to cleave the protective group, some tetrahydropyranyl ethers of conjugated dienols (**140**) or enones (**141**) have undergone total $C_3 \rightarrow C_4$ ring enlargement (equation 102)[131].



(102)

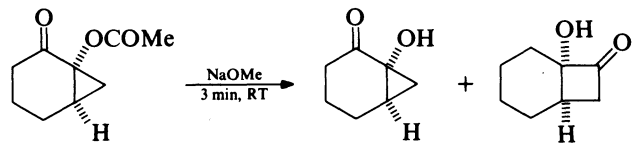
Likewise, tertiary allylic 1-hydroxycyclopropylcarbinol derivatives (**142**) and their vinylogous compounds (**143**) rearrange upon treatment with a catalytic amount of BF_3–Et_2O into 2-(hex-1-enyl)-2-methylcyclobutanone (**144**), a precursor of dihydrojasmone (**145**), obtained upon further acidic treatment with the Eaton's reagent ($MeSO_3H$–P_2O_5, 10:1) (equation 103)[174].



(103)

This stepwise $C_3 \rightarrow C_4 \rightarrow C_5$ ring expansion can be realized in a one pot reaction upon direct treatment of the tetrahydropyranyloxycyclopropane derivatives (**142** and **143**) with $MeSO_3H$–P_2O_5 (10:1), so providing an acid-induced $C_3 \rightarrow C_5$ ring enlargement competitive with the thermal $C_3 \rightarrow C_5$ rearrangement of vinylcyclopropane derivatives (*vide infra*, Section IV.A). An unexpected solvent effect has been reported in the lithium chloride-induced rearrangement of such 1-(1-hydroxycyclopropyl)carbinol derivatives[166].

Methoxide ion is also able to induce the ring expansion of 1-acetoxycyclopropylketone[175]. For instance, reaction of 1-acetoxybicyclo[4.1.0]heptan-2-one (**146**) with sodium methoxide at room temperature for 3 min resulted in the alcoholysis of the acetate and a partial (89%) $C_3 \rightarrow C_4$ ring enlargement to give a mixture of the isomeric acyloins **147** and **148** (equation 104)[176].

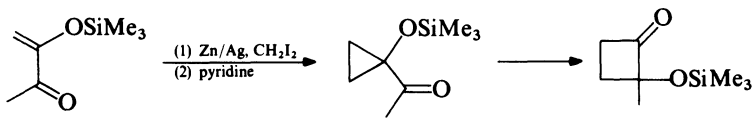


11% 89%

(146) (147) (148)

(104)

In a more complex transformation, the reaction of the monotrimethylsilyl enol ether of an α-dione (**149**) with the methylene iodide–Zn/Ag reagent results in the formation of 2-methyl-2-trimethylsiloxycyclobutanone (**151**), probably via the ring expansion of an intermediate (1-trimethylsiloxycyclopropyl) methyl ketone (**150**) (equation 105)[177].



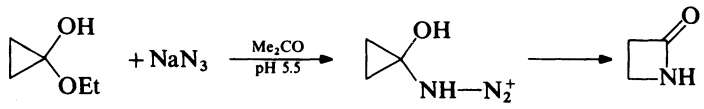
(149) (150) (151)

(105)

In conclusion, the $C_3 \rightarrow C_4$ ring enlargement of 1-hydroxycyclopropanecarboxaldehyde derivatives involve much milder conditions than those required with the 1-sulphide, 1-selenide or 1-methoxycyclopropane derivatives, reported in Section III.D.

F. 1-Aminocyclopropanol

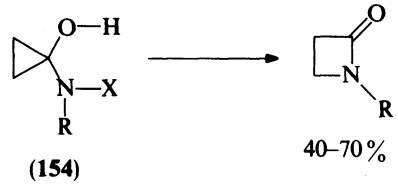
The ethyl hemiacetal of cyclopropanone (**152**)[32] reacts with sodium azide in buffered acetone (KH_2PO_4–NaOH) to form a β-lactam (**153**) (equation 106)[130].



(106)

(**152**) (**153**)

A related reaction occurs on chlorination of 1-aminocyclopropanol with *t*-BuOCl and subsequent treatment of (**154**) with silver ion in acetonitrile, from the reaction of the *O*-benzoyl derivative of 1-(*N*-*t*-butylhydroxylamino)cyclopropanol, or on tosylation of 1-hydroxy-aminocyclopropanol (equation 107)[178].



(107)

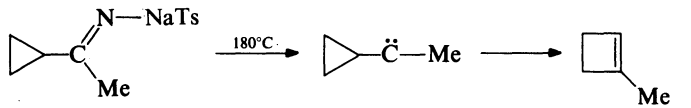
(**154**)

X = Cl, OCOPh, OTs

The importance of β-lactams in the penicillins[179], cephalosporins[180], thienamycin[181] and the recent discovery of antibiotic activity among monocyclic β-lactams[182] such as norcardicins[183] or the β-lactamase inhibitor clavulanic acid[184] have recently intensified research toward the synthesis of this system[184, 185]. Among the different procedures that have been developed for incorporating a 2-azetidinone unit[186], the ring expansion of cyclopropanol amines provides a simple and convenient route to these attractive small ring compounds.

G. Thermal

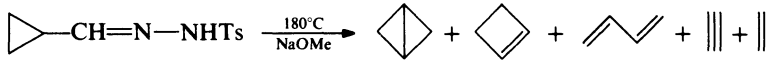
Besides the thermal rearrangement of 1-vinylcyclopropanols and of oxaspiropentanes (cf. Sections III.B and III.C) cyclopropane derivatives can undergo other kinds of $C_3 \rightarrow C_4$ ring expansion. For example, thermolysis at 180°C of the sodium salt of cyclopropylmethyl ketone tosylhydrazone (**155**) affords 1-methylcyclobutene (**156**) in 92% yield (equation 108)[187].



(108)

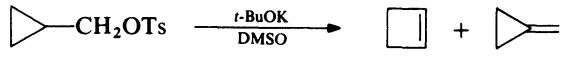
(**155**) (**156**)

Cyclopropanecarboxaldehyde *p*-tosylhydrazone (**157**) reacts with 0.8 equivalent of sodium methoxide in an aprotic solvent (triglyme) or with 1.1 equivalent of NaOMe in ethylene glycol at 180°C to give bicyclo[1.1.0]butane (57–90%) as a major product along with cyclobutene, 1,3-butadiene, acetylene and ethylene. On the other hand, decomposition by 1.1 equivalent NaOMe in triethylcarbinol gives mainly cyclobutene (95%) and decomposition by excess of sodium methoxide in diethyl carbitol gives cyclobutene (41%) and 1,3-butadiene (39%) (equation 109)[188].



(157) (109)

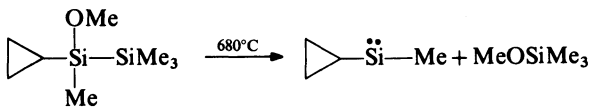
The sodium salt of cyclopropanecarboxaldehyde tosylhydrazone (**157**) behaves similarly on heating to 125–135°C. Labelling experiments using the lithium cyclopropanecarboxaldehyde-p-tosylhydrazone salt has proved the occurrence of a cyclopropylcarbene–cyclobutene $C_3 \rightarrow C_4$ ring expansion instead of a simple intramolecular carbene insertion in one of the four C–H bonds and bicyclobutane ring-opening[188]. For other examples and discussion of such a rearrangement see Ref. 189. In an apparently related reaction, when cyclopropylmethyl tosylate (**158**) is treated with potassium *t*-butoxide in dimethyl sulphoxide at room temperature for 1 h, a quantitative mixture of cyclobutene and methylenecyclopropane is produced in equal amounts (equation 110)[190].



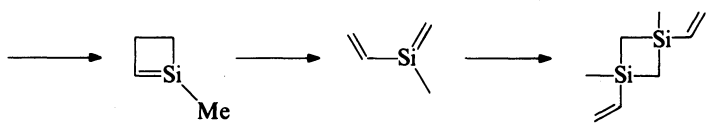
(158) 50% 50% (110)

However, the intermediacy of a cyclopropylcarbene from α-elimination was ruled out by labelling experiments. The rearrangement is assumed to proceed by a bimolecular eliminative mechanism[190]. For a recent convenient preparation of practically pure cyclobutene from cyclopropylmethanol, see Ref. 191.

Cyclopropylmethylsilene (**160**) obtained by thermal decomposition of 1-cyclopropyl-1-methoxytetramethyldisilane (**159**) at 680°C undergoes ring expansion to 1-methyl-1-silacyclobutene (**161**) which then undergoes ring-opening into vinylsilene and head to tail dimerization (equation 111)[192].

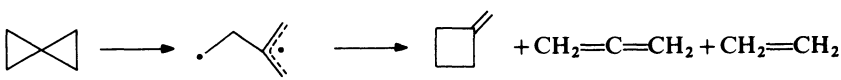


(159) (160)



(161) (111)

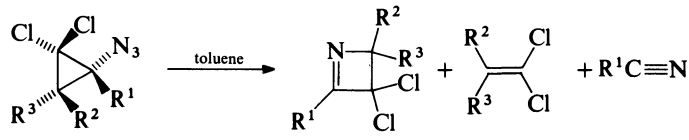
The pyrolysis of spiropentane at 386°C yields methylenecyclobutane (by C_3–C_4 ring expansion), ethylene and allene (by decomposition). The ratio of the products depends markedly on the total pressure of the system (equation 112)[193].



(112)

The mechanism involves either the intermediacy of a chemically activated, allylically stabilized biradical or a direct pathway without an intermediate[193]. The thermal $C_3 \rightarrow C_4$ ring expansion of methylenespiropentane leading to 1,2- and 1,3-dimethylenecyclobutane has been reported[44] (cf. Section II.E, equation 21).

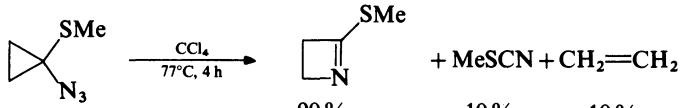
Cyclopropyl azides can lose nitrogen upon either heating at 100°C or irradiation to give highly reactive nitrenes which undergo ring expansion to 1-azetines and (or) elimination to olefins and nitriles[194, 195]. For example, 1-azido-2,2-dichlorocyclopropanes (**162**) decompose smoothly between 105 and 125°C in a highly regiospecific manner to give the corresponding 3,3-dichloroazetines (**163**) in 50–75% yields (equation 113)[194].



(113)

(**162**) (**163**)

In contrast, the photolysis of these azides at 350 nm leads only to the corresponding nitriles and olefins in yields of ~ 90%[194b]. 1-(Alkylthio)cyclopropyl azides (**164**), readily accessible from the corresponding chlorides and bromides, are smoothly decomposed at 77°C with nitrogen evolution. The main process is a ring enlargement to 2-(alkylthio)azetines (**165**), accompanied by cleavage to an alkyl thiocyanate and an alkene (equation 114)[196].



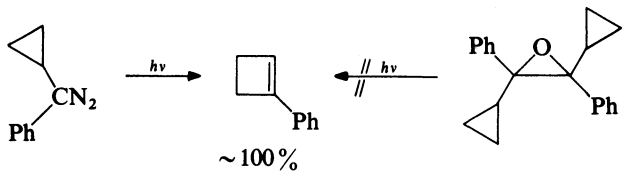
(114)

(**164**) (**165**)

The activation parameters suggest a two-step mechanism involving an intermediate cyclopropylnitrene. Again, the photolysis (300 nm) of these azides in CCl_4 gives exclusively the fragmentation products, the thiocyanate and the olefin[196].

H. Photochemical

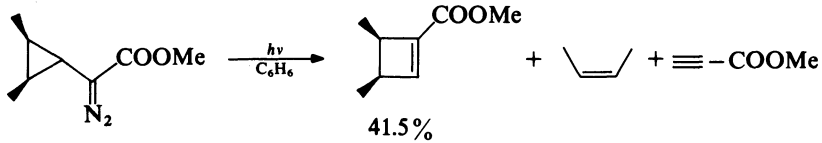
The phenylcyclopropylcarbene generated upon irradiation of phenylcyclopropyldiazomethane (**166**) in benzene, hexafluorobenzene or saturated and unsaturated hydrocarbons leads to 1-phenylcyclobutene (**167**) in nearly quantitative yield; on the other hand, the cyclopropylcarbene formed on irradiation of 2,3-biscyclopropylstilbene oxide (**168**) leads to secondary photo-products of higher molecular weights (equation 115)[197].



(115)

(**166**) (**167**) (**168**)

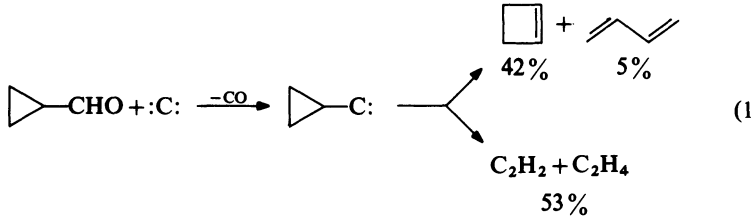
The direct irradiation of the methyl (*cis*-2,3-dimethylcyclopropyl)diazoacetate (**169**) in benzene for 3 h gives *cis*-3,4-dimethyl-1-carbomethoxycyclobutene (**170**) in 41.5% yield, together with methyl propiolate and *cis*-2-butene (equation 116)[198].



41.5%

(**169**) (**170**) (116)

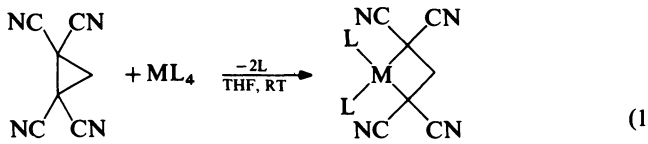
The *trans* diazoester behaves similarly. Thus both the ring expansion and fragmentation reactions proceed with retention of stereochemistry. The reaction most likely involves a concerted rearrangement[198]. In a related reaction, cyclopropylcarbenes have been generated by cocondensation of the corresponding cyclopropyl ketones with atomic carbon on a liquid nitrogen cooled surface. While cyclopropylcarbenes generated from the corresponding diazo compounds undergo minor fragmentation, the cyclopropylcarbenes from deoxygenation exhibit fragmentation as a major route to products (equation 117)[199].



(117)

I. Metal-promoted

It has been shown that electron-rich cyclopropanes are able to displace ethylene from dichloro(ethylene)platinum to yield four-membered metallocyclic complexes[76] (cf. equation 37). On the other hand 1,1,2,2-tetracyanocyclopropane (**171**) reacts under mild conditions with zerovalent platinum and palladium complexes of the type $Pt(PPh_3)_2(C_2H_4)$ or ML_n ($n = 3, 4$; M = Pd or Pt; L = phosphines or triphenylarsines) to give metallocyclobutane derivatives (**172**) (equation 118)[200].

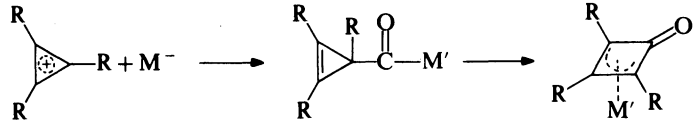


50–80%

(**171**) (**172**) (118)

The reaction proceeds via a nucleophilic attack of the ML_4 moiety on the carbon atom bearing the cyano groups. An alternative mechanism would involve a possible dissociation of tetracyanocyclopropane (**171**) to give a biradical[200]. Reactions of cyclopropenyl cations

(**173**) with metal carbonyl anion afford η^3-oxocyclobutenyl complexes (**175**) in an intriguing reaction by which CO is incorporated into the three-membered ring[201]. It has been shown that the mechanism involves electrophilic attack at a CO ligand rather than at cobalt to afford an intermediate, coordinatively unsaturated, cyclopropenyl carbonyl metal species (**174**) which then undergoes $C_3 \rightarrow C_4$ ring expansion (equation 119)[202].

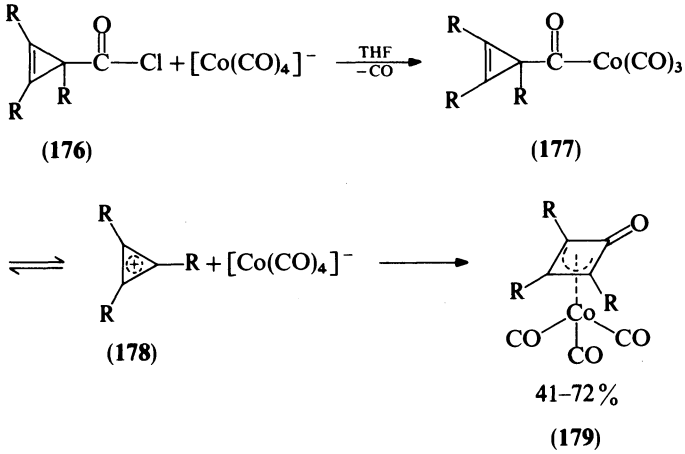


(119)

(**173**) (**174**) (**175**)

M = $Co(CO)_4$, $Fe(CO)_3NO$, $Fe(C_5H_5)(CO)_2$

This mechanism was evidenced by the reaction of 2-cyclopropene-1-carbonyl chlorides (**176**) with $[Co(CO)_4]^-$ in MeCN, THF or C_6H_6 which affords (η^3-oxocyclobutenyl)tricarbonyl cobalt complexes (**179**) (equation 120)[203].



(120)

(**176**) (**177**) (**178**)

41–72%

(**179**)

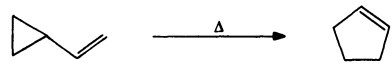
The reaction was shown to proceed by formation of a coordinatively unsaturated (3-cyclopropen-1-yl carbonyl)tricarbonylcobalt (**177**) in dynamic equilibrium with a cyclopropenium cation (**178**) and $[Co(CO_4)]^-$. The effects of ring substituents on the selectivity of the cobalt-promoted C–C bond cleavage in the ring expansion step resemble those obtained in photochemical rather than thermal ring-openings of cyclopropenes[204], i.e. cleavage adjacent to alkyl rather than aryl is observed[203].

IV. $C_3 \rightarrow C_5$ RING ENLARGEMENTS

A. Vinylcyclopropane–Cyclopentene

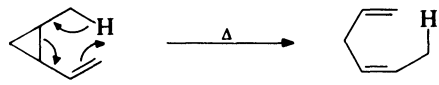
1. Thermal

The thermal vinylcyclopropane–cyclopentene rearrangement discovered by Neureiter in 1959[205] has been the subject of many mechanistic and theoretical studies (equation 121)[206].



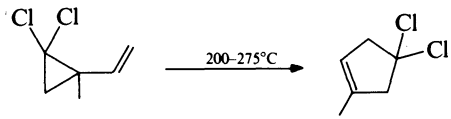
(121)

The substituents attached to the vinylcyclopropane moiety may have a drastic effect upon the reaction path. For example, a methyl placed on the cyclopropane ring *cis* to the vinyl group orients the reaction to a 1,5-hydrogen shift (equation 122)[207].



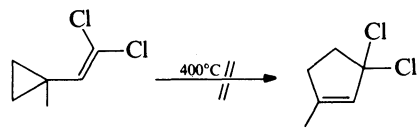
(122)

Heteroatoms, depending upon their location, have varied effects. Thus, for instance, the pyrolysis of 1,1-dichloro-2-methyl-2-vinylcyclopropane (**180**) at 200–275°C yielded exclusively 1-methyl-4,4-dichlorocyclopentene (**181**) whereas its isomer, 1,1-dichloro-2-(1-methylcyclopropyl)ethylene (**182**) was remarkably stable up to 400 °C (equation 123)[208].



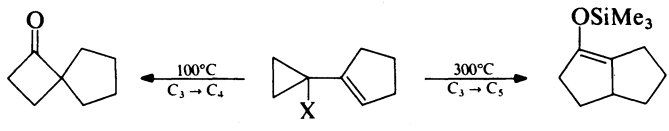
(**180**) (**181**)

(123)



(**182**)

While l-vinylcyclopropanols undergo thermal rearrangement to cyclobutanones[132] (see Section III.B) an alternate pathway is followed when the hydroxyl group is protected with a trimethylsilyl ether linkage. So, 1-(1-cyclopentenyl)cyclopropanol **183a**) undergoes on heating at 100°C quantitative $C_3 \rightarrow C_4$ ring enlargement into spiro[3.4]octan-1-one (**184**)[132], whereas its *O*-silylated derivative (**183b**) undergoes the thermal $C_3 \rightarrow C_5$ vinylcyclopropane–cyclopentene rearrangement into the regiospecific silyl enol ether of bicyclo [3.3.0]octan-1-one (**185**) (equation 124)[99, 145, 209].



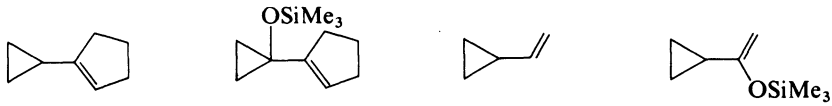
(**184**) (**183**) (**185**)

a: X = OH
b: X = $OSiMe_3$

(124)

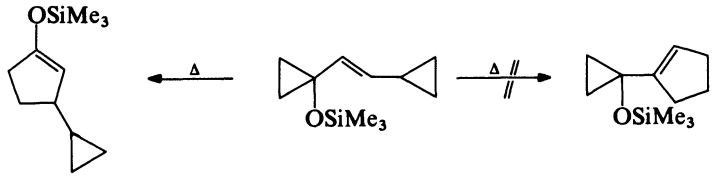
Usually the activation free energy required for the thermal vinylcyclopropane–cyclopentene rearrangement ranges from 48 to 53 kcal mol^{-1} [210]. A quantitative treatment of the substituent effect has been conducted[211]. It appears that the trimethyl-

siloxy effect, which is very similar to the methoxy effect, is also highly dependent on the position of this substituent in the system. When placed on the cyclopropane ring, this substituent facilitates the rearrangement by 4.9 kcal mol^{-1} [211]. However, placed on the double bond it hampers the rearrangement by 3 kcal mol^{-1} [211, 212].



$\Delta G^{\ddagger}$ = 48.7 (kcal mol^{-1}) 43.8 48.2 51.3

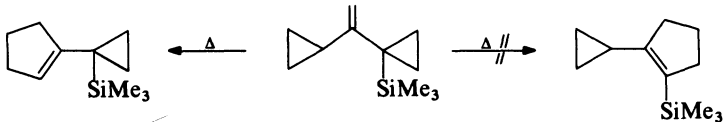
Several rationales for the high $\Delta G^{\ddagger}$ for the rearrangement of the silyl enol ether of cyclopropylmethyl ketone can be proposed: reduction of the π electrons' participation in the ring-opening, inductive destabilization of any radicaloid species or no significant relief of steric strain upon ring-opening[211]. Whatever it may be, this substituent effect is responsible for the high regiospecificity of the rearrangement. As a matter of fact, when two vinyl cyclopropane moieties as in **186** can be *a priori* involved in the rearrangement, the driving substituent effect of the siloxy group leads exclusively to the 3-cyclopropylcyclopentanone silyl enol ether (**187**) (equation 125)[213].



(125)

(187) **(186)**

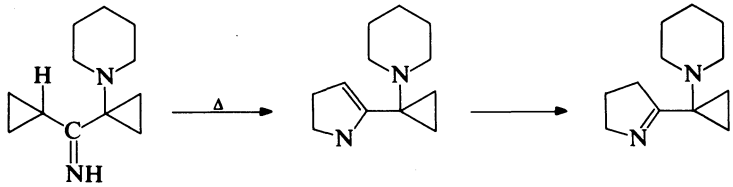
On the other hand, the trimethylsilyl substituent which is known to destabilize an α-radical[214] has an opposite effect. Thus, it has been observed that the pyrolysis at 570 °C of 1-(1-(trimethylsilyl)cyclopropyl)-1-cyclopropylethylene (**188**) leads exclusively to 1-(1-(trimethylsilyl)cyclopropyl)cyclopentene (**189**)[215]. Contrary to the siloxy group, the silyl substituent exerts a rate-retarding effect on the rupture of the cyclopropane ring (equation 126).



(126)

(189) **(188)**

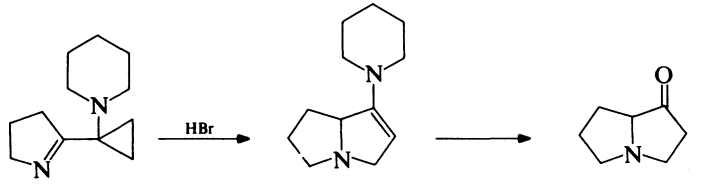
A similar exclusive participation of the less substituted cyclopropane ring has also been reported in the thermal rearrangement of 1-(1-piperidinocyclopropyl)-1-cyclopropylketimine (**190**). On heating in xylene, the imine undergoes ring enlargement similar to the vinylcyclopropane–cyclopentene ring enlargement into the enamine (**191**), followed by isomerization into the cyclic imine tautomer (**192**) (equation 127)[216].



(127)

(190) (191) (192)

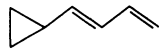
Although prolonged heating of the pyrroline (**192**) does not lead to further ring expansion, a second cyclopropylimine rearrangement takes place on heating in the presence of anhydrous hydrobromic acid at 140°C for 10 min, giving after hydrolysis the pyrrolizidinone (**193**) (equation 128)[216]. This sequence opens a route to pyrrolizidines that are of obvious interest in natural product synthesis.



(128)

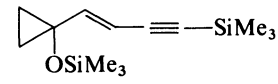
(192) (193)

The conjugation of the vinylic bond of the vinylcyclopropane system with unsaturated substituents also lowers the required activation energy of the thermal rearrangement: for instance, 44.5 kcal mol^{-1} has been measured for the rearrangement of the butadienylcyclopropane (**194**)[210].



(194)

E_a = 44.5 kcal mol^{-1}



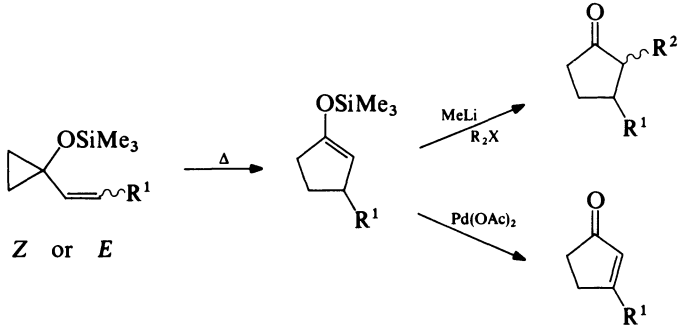
(195)

40 kcal mol^{-1}

Additional conjugation and trimethylsiloxy effects have been observed; so, the activation energy required for the rearrangement of 1-trimethylsiloxy-1-(4-trimethylsilyl-1-buten-3-ynyl)cyclopropane (**195**) was estimated to be 40 kcal mol^{-1} [213].

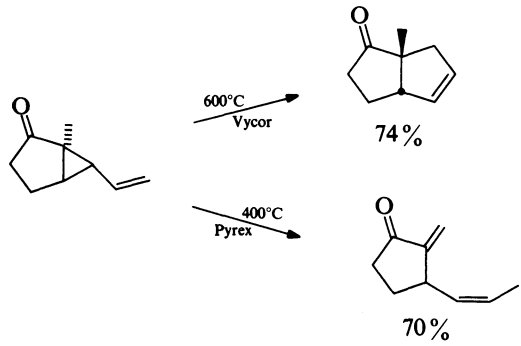
The thermal $C_3 \rightarrow C_5$ ring expansion of 1-siloxy-1-vinylcyclopropanes occurs either from the *Z* or from the *E* isomers. It leads to cyclopentanone silyl enol ethers that are able to undergo either further regiospecific alkylation into 2,3-disubstituted cyclopentanones[32, 145, 209, 213] or dehydrosilylation into cyclopentenones[131, 146]. The overall process constitutes an efficient three-carbon annelation process (equation 129).

The synthesis of cyclopentanoid compounds is a subject of current interest due to the discovery of a growing number of naturally occurring substances of biological importance containing the five-membered ring moiety[217]. Among the different methodologies this rearrangement constitutes an efficient new synthetic tool[218–222]. It has been illustrated by the total synthesis of the 11-deoxyprostaglandin E_2[213], of aphidicolin[223] and by the preparation of some spirovetivane derivatives[131].



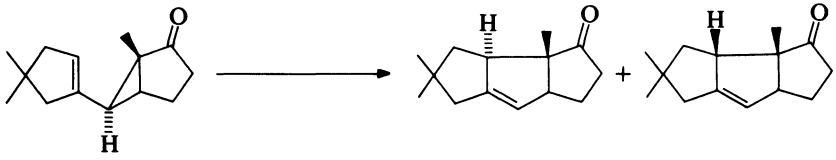
(129)

Usually the reaction occurs either on heating the vinylcyclopropane in the liquid phase in a sealed tube at 300°C for 30 min[209, 213] by passing it through a conditioned hot tube at 330°C with a contact time of 4 s[145] or by flash thermolysis at 600°C for 10 ms[213, 223]. However, careful choice of the pyrolytic conditions may be necessary. Thus, as shown in equation 130, thermolysis in lead conditioned Vycor glass at 580°C or in Pyrex glass at 400°C, leads either to the expected bicyclic ketone or to a retroene product[224].



(130)

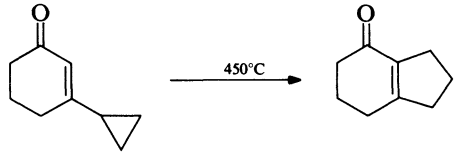
Enhanced stereoselectivity was observed in a rhodium–promoted bond reorganization. Whereas an equal mixture of epimers was obtained at 560°C, the formation of the *cis, syn, cis* fused epimer was totally suppressed after initial complexation of the vinylcyclopropane (**196**) with $(C_2H_4)_2Rh$ (acac) and heating at 80–180°C only (equation 131)[224].



	Vycor/$PbCO_3$	560°C	70%	(50 : 50)
	$(C_2H_4)_2Rh$(acac)	180°C	68%	(100 : 0)

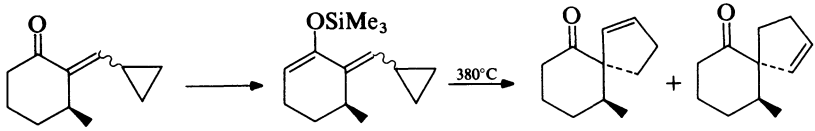
(131)

The thermolysis of β-cyclopropylenones has also produced cyclopentenes (equation 132)[225].



(132)

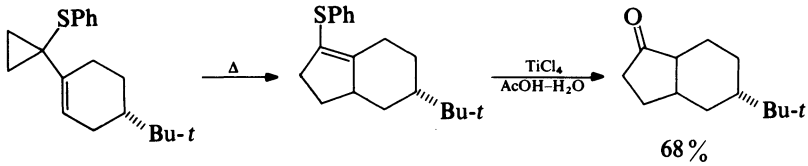
However, the synthesis of spiro compounds requires the preparation of silyl enol ethers prior to the thermolysis (equation 133)[226].



57% (2.5 : 1) (133)

This methodology has been applied to the synthesis of some spirovetivane-type sesquiterpenoids[226] and of (±) zizaene[227].

1-(Thiophenyl)vinylcyclopropanes (**197**) (see Section III.D) undergo thermal ring enlargement into the enol thioethers of cyclopentanone (**198**) (equation 134).

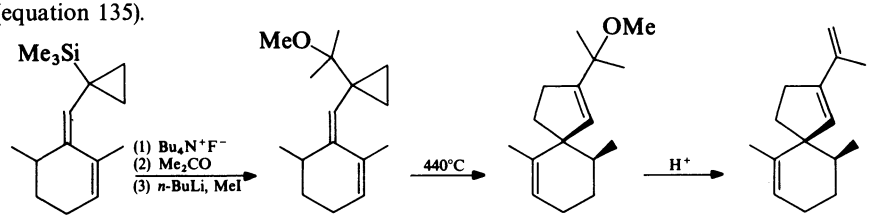


68%

(**197**) (**198**) (**199**) (134)

Then, hydrolysis with $TiCl_4$, acetic acid and water at room temperature led to the expected cyclopentanone (**199**)[228]. The stereochemistry of the newly formed C–C bond in the six-membered ring is equatorial, which contrasts with the results obtained in the Claisen rearrangements[229].

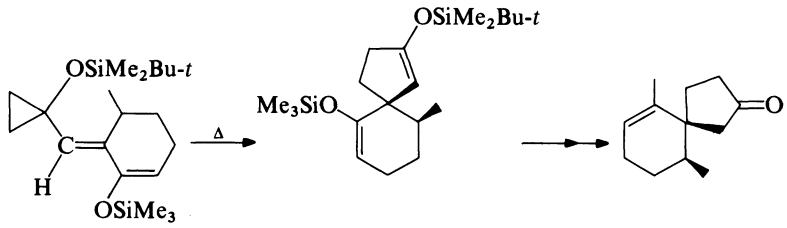
1-Trimethylsilylcyclopropane derivatives, in spite of the retarding effect of the silyl substituent on the vinylcyclopropane rearrangement (see equation 125), constitute also useful intermediates because the silicon cyclopropyl carbon bond can be efficiently substituted by a carbon–carbon bond[230]. Thus, coupling of α-trimethylsilyl-cyclopropanecarboxaldehyde with 2,6-dimethyl-2-cyclohexen-1-one in the presence of Ti(O) provided a silylated vinylcyclopropane (**200**)[231], which, after desiliconation by means of Bu_4NF, electrophilic alkylation and highly stereoselective $C_3 \rightarrow C_5$ thermal ring enlargement, has been transformed into α-vetispirene (**201**)[230], hinesol and β-vetivone[231] (equation 135).



(**200**) (**201**)

(135)

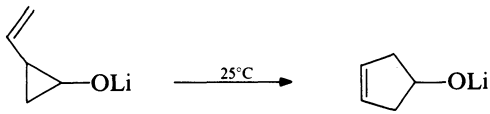
However, a dispatch route to the [4.5]spirocyclic sesquiterpenes of the spirovetivane type has been recently reported from the readily available α-siloxycyclopropanecarboxaldehyde, via the stereospecific thermal ring enlargement of a silylated 1-vinylcyclopropanol (**202**) (equation 136)[131c].



(**202**) (**203**) (136)

The resulting spiro[4.5]decen-2-one (**203**) is not only a constituent of Vetiver oil of economical importance but also constitutes the key intermediate for the synthesis of other spirovetivane–sesquiterpenes[131c].

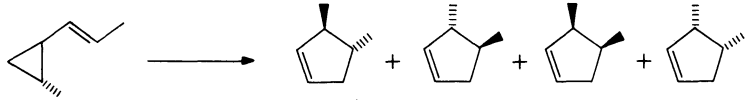
Alkoxy-2-vinylcyclopropanes rearrange stereospecifically to 2-cyclopentenols under very mild conditions. Thus, the lithium salt of 2-vinyl-1-cyclopropanol (**204**) undergoes the vinylcyclopropane–cyclopentene rearrangement at room temperature (equation 137)[232].



(**204**) (137)

This accelerated 2-alkoxy vinylcyclopropane rearrangement generally proceeds with remarkably high stereoselectivity, providing a stereoselective method for the conversion of 1,3-dienes to cyclopentene derivatives in a one pot reaction[233a]. Likewise, 2-carbonism substituted vinylcyclopropanes provide cyclopentenes at $-30°C$[233b]. Unfortunately, although the oxy–Cope rearrangement is 10^{10}–10^{17} times accelerated by potassium alkoxide[234], such a dramatic rate enhancement was not observed with the potassium salts of 1-vinylcylopropanols and with the potassium enolates of cyclopropyl ketones[32].

In order to define the stereochemical characteristics of the cyclopentene forming reaction, the thermal isomerization of optically pure (+)(1*S*,2*S*)-*trans*,*trans*-2-methyl-1-propenylcyclopropane (**205**) has been investigated (equation 138).



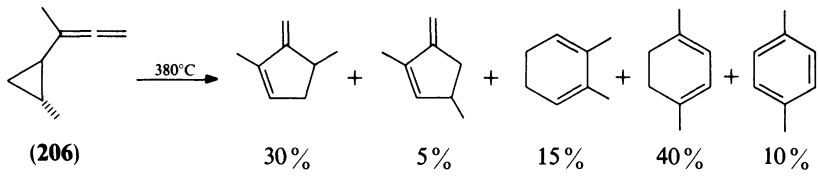
(**205**)

si, 65% (−) −A + ar, 8% (+) −A + sr, 22% (−) −B + ai, 5% (+) −B (138)

The high degree of retention of optical purity (80.1 ± 0.4% and 68.8 ± 0.5% on heating at 296.5°C for 60 and 120 min, respectively), in both the allowed products A and the forbidden products B rule out the possibility of freely rotating diradical intermediates in

the thermal $C_3 \rightarrow C_5$ ring enlargement of this vinylcyclopropane system. Four concerted processes, two allowed and two forbidden, with the possible intervention of a planar π-vinylcyclopropane intermediate, having an orbital structure appropriate for disrotatory ring closure had been suggested[235].

Thermal isomerization of 3-(*trans*-2-methylcyclopropyl)-1,2-butadiene (**206**) produces dimethylenecyclopentenes, dimethylcyclohexadienes and *p*-xylene (equation 139).

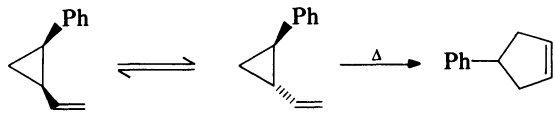


(**206**) 30% 5% 15% 40% 10%

(139)

These products emanate from *trans* to *cis* isomerization of the methylcyclopropyl allene (**206**) which competes with cyclopentene formation and a facile [1.7]hydrogen migration[236].

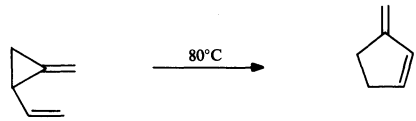
At 140–150°C *cis*-1-phenyl-2-vinylcyclopropane (**207**) undergoes *cis* $\rightleftharpoons$ *trans* interconversion and above 200°C ring enlargement into 4-phenylcyclopentene (**208**) is observed (equation 140)[237].



(**207**) (**208**) (140)

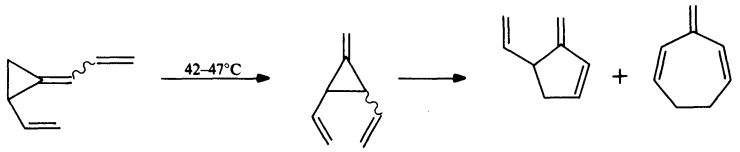
Cope rearrangements, i.e. [3,3]sigmatropic shifts, can be obtained competitively to the $C_3 \rightarrow C_5$ ring expansion, i.e. the [1,3]sigmatropic shift[238]. For instance, *cis*-1,2-divinylcyclopropane undergoes rearrangement into 1,4-cycloheptadiene below room temperature[239] while its *trans* isomer undergoes *trans* $\rightleftharpoons$ *cis cis* isomerization and the same $C_3 \rightarrow C_7$ ring enlargement upon heating at 170°C[240].

Vinylmethylenecyclopropane (**209**) undergoes thermal rearrangement into 3-methylenecyclopentene (**210**) on heating at 80°C for 13 h (equation 141)[241].



(**209**) (**210**) (141)

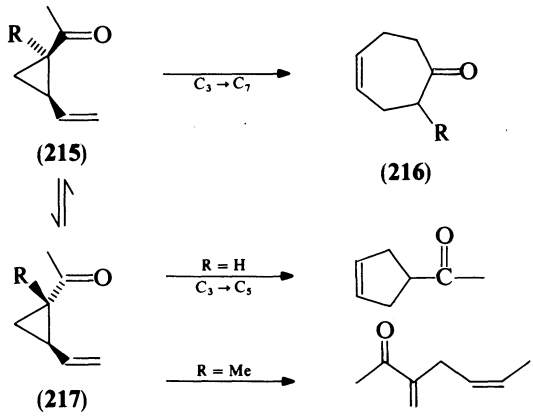
The moderate conditions required for this conversion (E_a = 25.8 kcal mol^{-1}) suggest that a planar diradical is not an appropriate intermediate[242]. The interconversions of several vinylmethylenecyclopropanes have been studied and [1,3]sigmatropic shifts can alone account for all the products, although some [3,3]shifts are not excluded[241]. For example, the *syn* and *anti* isomers of 1-allylidene-2-vinylcyclopropane (**211**) undergo thermal isomerization into 4-vinyl-3-methylenecyclopentene (**213**) and 3-methylene-1,4-cycloheptadiene (**214**) on heating in cyclohexane at 42–47°C (equation 142).



(142)

(211) (212) (213) (214)

It is likely that the conversion involves a methylenecyclopropane rearrangement into 2,3-divinylmethylenecyclopropane (**212**)[243], followed by a [1,3]sigmatropic process or a Cope rearrangement which leads to the $C_3 \rightarrow C_5$ and $C_3 \rightarrow C_7$ ring enlargement products, respectively. *Cis*-(2-Vinylcyclopropyl)methyl ketones (**215**) undergo on heating at 220°C ring enlargement into cyclohepta-4-en-1-one (**216**) and isomerization into *trans*-1-acetyl-2-vinylcyclopropanes (**217**) which then undergo either $C_3 \rightarrow C_5$ ring enlargement or ring-opening depending on the nature of the substituent R (equation 143)[244].

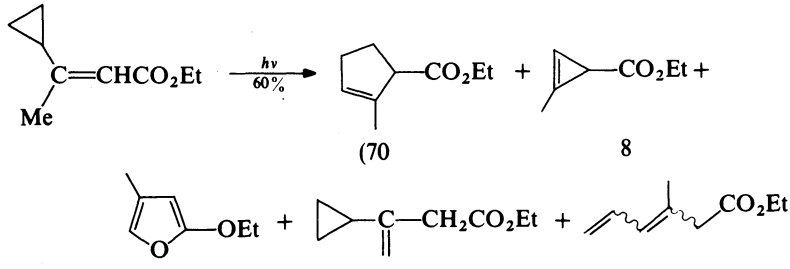


(143)

It must be emphasized that no heterocyclization occurs and that the formation of the cycloheptenone involved the enolization of the carbonyl group of the methylcyclopropyl ketone.

2. Photochemical

The photochemical counterpart of the thermal vinylcyclopropane rearrangement has been described[245].

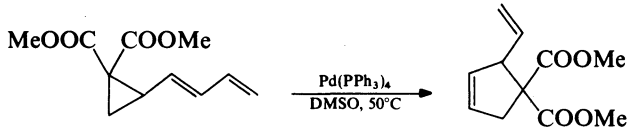


(144)

Thus, vinylcyclopropanecarboxylates undergo upon direct photolysis either ring expansion into cyclopentenes or fragmentation to carbenes which then can collapse to allenes, furans and cyclopropenes in 60% isolated yields (see for instance equation 144)[246]. Sensitized photolyses (acetone, xanthone or benzophenone in benzene, or triphenylene) yield only cyclopentenes. The photolytic course is strongly influenced by the double bond substituents; thus the ability to undergo the photochemical vinylcyclopropane rearrangement is clearly related to the presence of an α-methyl substituent in the cyclopropylacrylic ester[246]. Although photochemically induced vinylcyclopropane rearrangements are common in cyclic systems[245d], vinylcyclopropane[247] and 1-(2,2-dimethyl-3-phenylcyclopropyl)-2-methylpropane[248] have been reported not to undergo the expected ring enlargement. It must be emphasized that the reverse reaction, i.e. the ring contraction of cyclopentene to a vinylcyclopropane, occurs upon irradiation[247].

3. Metal-promoted

Dienylcyclopropanes (**218**) activated by two electron-withdrawing groups easily rearrange to vinylcyclopentene derivatives (**219**) in the presence of a catalytic amount of Pd(O) at 25–60°C (equation 145)[249].



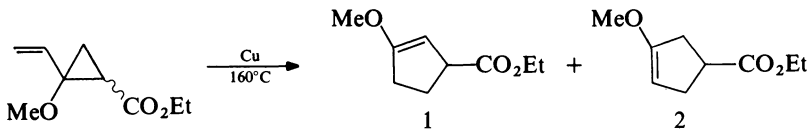
87%

(145)

(**218**) (**219**)

The presence of the two electron-withdrawing groups and dienic moiety is essential for the rearrangement which might proceed through nucleophilic attack of Pd(O) to the dienic moiety to form a π-pentadienyl palladium and stabilized anion moieties resulting from cyclopropane cleavage[250]. The intermediate then collapses to form cyclopentene derivatives and the new C–C bond formation exclusively produces a five-membered ring and not a seven-membered one[251]. This method provided a simple route to terpenic cyclopentanoids such as dolichodial and iridodiol[249].

On heating at 160°C in the presence of catalytic amounts of copper bronze or copper(I) chloride, ethyl 2-methoxy-2-vinylcyclopropanecarboxylates (**220**) undergo ring expansion into the isomeric 3-methoxy-2-cyclopentene (**221**) and 3-methoxy-3-cyclopentenecarboxylates (**222**) equation 146); on the other hand platinum and rhodium complexes catalyse the ring-opening into ethyl-4-methoxy-3,5-hexadienoate[252].



1 2

(146)

(**220**) (**221**) (**222**)

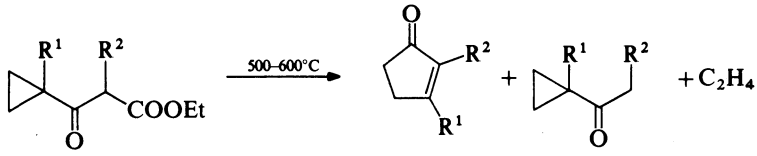
B. Not Involving the Vinylcyclopropane Moiety

There are relatively fewer examples of $C_3 \rightarrow C_5$ cyclopropane ring enlargements which do not involve the vinylcyclopropane moiety. Most of them lead to thermal or

photoinduced heterocyclization, involve a photochemical rearrangement of cyclopropene derivatives or an insertion of a transition metal into the carbon–carbon bond of electronegatively substituted cyclopropanes (cf. Section II.G). The solvolytic formation of spirocyclopropylcarbinyl cations may also lead to ring enlargement products.

1. Thermal

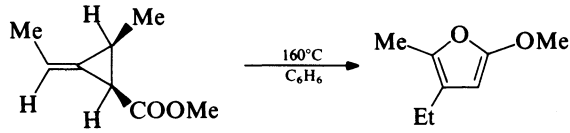
The pyrolysis of 3-cyclopropyl-3-oxopropanoates (**223**) at 500–600°C gives 2-cyclopentenones in 50–80% yields and cyclopropyl ketones (equation 147)[253].



(223) $+CO+CO_2+EtOH$ (147)

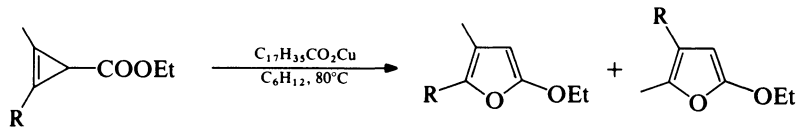
The substitution pattern of the cyclopentenones requires the loss of the oxo group rather than of the carbonyl of the carboxyl group. The mechanism is believed to consist of the formation of an acylketene with subsequent thermally allowed π 2s + π 2a electrocyclic reaction leading to an intermediate cyclopropanone which then undergoes carbon monoxide elimination[253].

On heating at 160°C in dry benzene for 48 h, 2-carbomethoxy-3-methylethylidenecyclopropane (**224**) undergoes hetero ring enlargement into 4-ethyl-2-methoxy-5-methylfuran (**225**) (equation 148)[254].



(224) (225) (148)

Such 2-alkoxyfurans have also been obtained on heating 3-carboethoxy cyclopropenes (**226**) at 80°C for 1 h in the presence of copper salts.



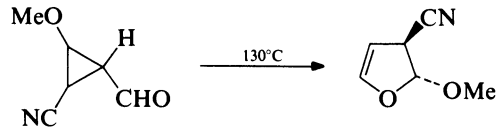
(226)

R = Ph	95%	5%
n-Bu	50%	50%
t-Bu	55%	45%

(149)

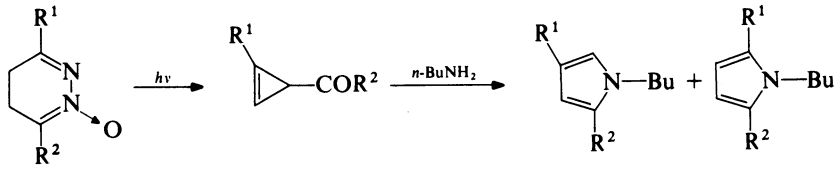
When R = phenyl, the rearrangement is regiospecific (equation 149)[204,255].

1-Cyano-2-methoxycyclopropane-3-carboxaldehyde (**227**), formed by photolysis of 2-cyanofuran in methanol at 254 nm, rearranges thermally on heating at 130°C for 10 min to *trans*-2-methoxy-3-cyano-2,3-dihydrofuran (**228**) (equation 150)[256].



(227) (228) (150)

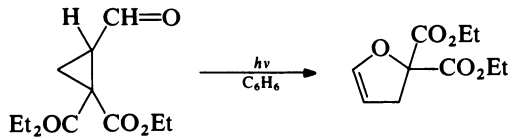
When 3-cyclopropenyl ketones (**230**), formed by irradiation of pyridazine *N*-oxides (**229**), were heated with *n*-butylamine under reflux for 1 h or stirred at room temperature for 3–4 h a mixture of pyrroles was formed in 80% yield (equation 151)[257].



(229) (230) (151)

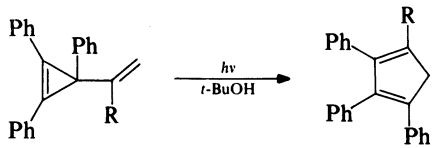
2. Photochemical

Photolysis in benzene of 2,2-diethoxycarbonylcyclopropanecarboxaldehyde (**231**) leads to diethyl-2,3-dihydrofuran-2,2-dicarboxylate (**232**) (equation 152)[57].



(231) (232) (152)

3-Vinylcyclopropenes have been found to rearrange photochemically to cyclopentadienes. Thus, irradiation of 1,2,3-triphenyl-3-vinylcyclopropene (**233**) in *t*-BuOH using a 450 W medium pressure lamp and a Pyrex filter for 3.5 h afforded 1,2,3-triphenylcyclopentadiene (**234**) in 87% yield (equation 153)[258].

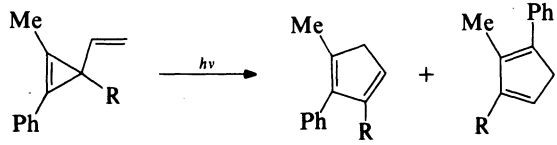


R = H, Ph 87% (153)

(233) (234)

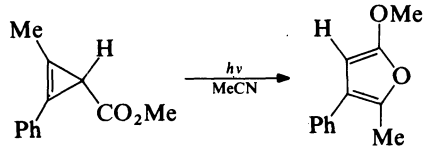
Terminal methyl substitution on the vinyl group inhibits the reaction but phenyl substitution at the α-carbon of the vinyl group (R = Ph) as well as phenyl substitution at carbon-1 of the cyclopropene ring were found to enhance the reactivity[258].

The photochemical rearrangement of 3-vinylcyclopropenes exhibits some regioselectivity. Thus, contrary to the selectivity observed with the thermal rearrangement of cyclopropenecarboxylates (see equation 149), the major product obtained from the irradiation of unsymmetrical substituted cyclopropenes was derived from the preferential cleavage of the cyclopropene single C–C bond which is methyl rather than phenyl substituted (equation 154)[259].



2.5 1 (154)

Similar regioselectivity was observed upon photolysis of methyltriphenylcyclopropenes[257]. The photochemistry of methyl 1-methyl-2-phenylcyclopropene-3-carboxylate (**235**) has been examined in both the racemic and optically active forms. In the excited singlet (irradiation in MeCN) the cyclopropene is converted to 2-methoxy-5-methyl-4-phenylfuran (**236**) (equation 155).

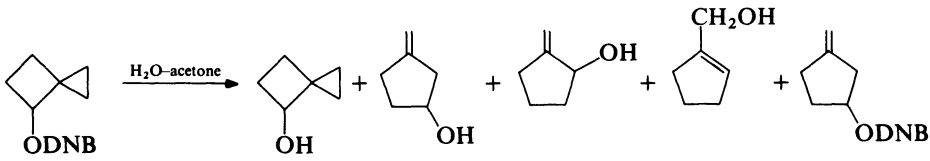


(**235**) (**236**) (155)

On the other hand, in the triplet state (irradiation in acetone or acetonitrile in the presence of benzophenone) the cyclopropene dimerizes into a tricyclohexane derivative. Moreover, racemization occurs about 2.5 times faster than conversion to the furan product, indicating the intermediacy of a vinylcarbene on the singlet surface, whereas no racemization is observed in the triplet state[260].

3. Solvolytic

The solvolysis of spiro[2.*n*]alkan-4-ol derivatives leads to ring enlargement products. In particular, solvolysis of spiro[2.3]hexyl-4-(3′,5′-dinitrobenzoates) (ODNB) (**237**) in 80% aqueous acetone gives a mixture of five-membered ring compounds derived from $C_3 \rightarrow C_5$ ring expansion (equation 156)[261a].



(**237**) 16% 52% 15% 5% 10% (156)

The same products were obtained in the solvolysis of 4-chlorospirohexane[261b], 1-methyl-bicyclo[2.1.0]pentyl *p*-nitrobenzoate[262], 1-cyclobutenylethyl tosylate and 1-methyl-bicyclo[1.1.1]pentyl dinitrobenzoate[262], suggesting that the bicyclo [2.1.0]pentane-1-methyl cation is the common intermediate.

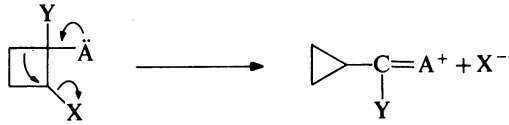
V. $C_4 \rightarrow C_3$ RING CONTRACTIONS

A. Cyclobutyl Cation

Since the pioneering observation of Demjanov that both cyclobutylamine and cyclopropylcarbinylamine react with nitrous acid to give a mixture of cyclobutanol and cyclopropylcarbinol[263], the facile interconversions which occur among related cyclobutane, cyclopropane and open-chain structures via carbenium ion intermediates have been extensively studied. This question has been discussed in Section III.A; for a review concerning the formation, structure and ring contraction of cyclobutyl cations, see Ref. 264.

B. Not Involving Carbenium Ion

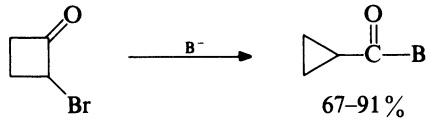
The reactions of cyclobutyl derivatives, involving carbenium ion intermediates, afford mixtures of cyclobutyl, cyclopropylmethyl and 3-butenyl compounds, and are therefore of limited synthetic applicability[265]. However, the presence of an electron-donating group (A) attached to one ring carbon atom, and vicinal to the carbon bearing the leaving group (X) provides a system which undergoes thermal, acid- or base-catalysed ring contraction leading to a single product, in high yields (equation 157).



(157)

1. 2-Halocyclobutanone

The first reaction reported in this category was the ring contraction of 2-bromocyclobutanone into cyclopropanecarboxylic acid or derivatives. It occurs with high yield and stereospecificity, under the action of aqueous sodium carbonate, sodium ethoxide in ethanol or ether, liquid ammonia or even boiling water (equation 158)[266].

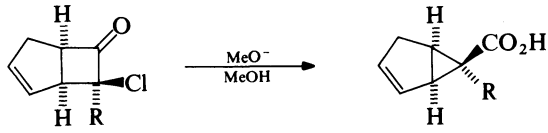


(158)

B = base

Among the four mechanisms advanced for the Favorskii rearrangement of α-haloketones, only the semibenzilic acid mechanism was found to be consistent with the stereochemical, kinetic and labelling evidence of the ring contraction of 2-bromocyclobutanones[267]. The reaction takes place stereospecifically with inversion of configuration at the carbon bearing the leaving group, and this leaving group must be able to assume a pseudoequatorial conformation[267]. The ring contraction may equally be effected by $LiAlH_4$ or methylmagnesium iodide[163]. The nucleophile-induced reaction of *endo*-7-halobicyclo[3.2.0]hept-2-en-6-one (**238**) and related ketones, readily available from

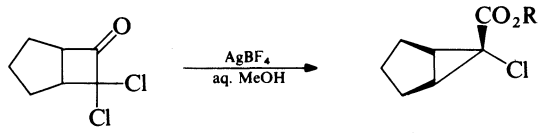
haloketenes and cyclopentadienes, leads exclusively to the ring-contracted acids (equation 159)[268].



(159)

(238)

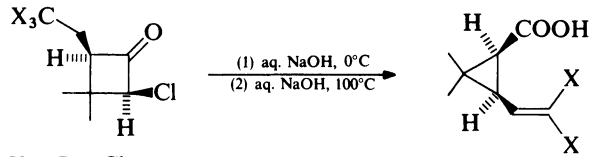
In general, α,α-dihalocyclobutanones do not undergo the ring contraction in the presence of nucleophiles but suffer cleavage instead[269]. It has been reported, however, that 7,7-dichlorobicyclo[3.2.0]heptan-6-one (**239**) affords exclusively *exo*-6-chlorobicyclo [3.1.0] hexane *endo*-6-carboxylic acid (R = H) and ester (R = Me) (**240**) in 24 and 11.5% yield respectively, upon treatment with silver tetrafluoroborate in boiling aqueous methanol (equation 160)[270].



(160)

(239) (240)

Useful applications of this ring contraction of α-halocyclobutanones have been reported, in particular in the field of pyrethrins and pyrethroids[271]. For instance, biologically interesting dihalovinylcyclopropanecarboxylic acids (**242**) have been obtained from optically active α-halocyclobutanones (**241**) by a stereospecific $C_4 \rightarrow C_3$ ring contraction and subsequent elimination of HX (equation 161)[271]. (To date twelve patents are based on the ring contraction of α-halocyclobutanones.)



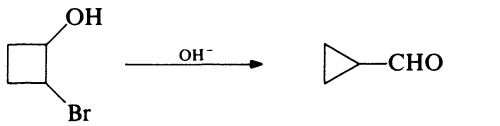
(161)

X = Br, Cl

(241) (242)

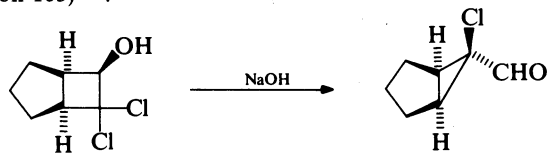
2. 2-Halo- and 2-tosyloxycyclobutanol

2-Bromo- and 2-tosyloxycyclobutanols prepared by $LiAlH_4$ reduction of the corresponding ketones[163] or acetates[272] undergo quantitative transformation into cyclopropanecarboxaldehydes upon treatment with aqueous sodium hydroxide, boiling water or in a refluxing water–methanol mixture (equation 162).



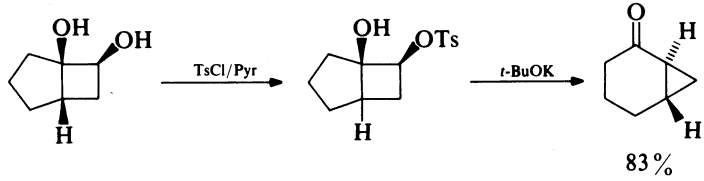
(162)

Ring contraction of α-halocyclobutanols forming part of bicyclic systems has been also reported (equation 163)[273].



(163)

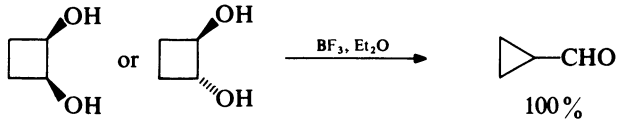
The reactions are stereospecific with respect to the configuration of the hydroxyl group, *exo*-alcohols giving *endo*-aldehydes and *vice versa*. Since, in the related ring contraction of 2-halocyclobutanones (see Section V.B.1) the reaction occurs with inversion of configuration at the halogen-bearing carbon, it is presumably the chlorine atom *trans* to the hydroxyl group which is displaced. The reaction is not promoted by silver salts, indicating that carbenium ions are not involved[273]. It has also been shown that the reactions of the monochlorocyclobutanols are stereospecific with respect to the configuration of the halogen atom and that contraction can only occur if this atom is able to adopt a pseudo-equatorial conformation. When this is sterically hindered, a 1,2-hydrogen shift occurs instead[274]. For other examples of ring contraction of bicyclic and spiro 2-halocyclobutanols, see Ref. 275. Bicyclic 2-tosyloxycyclobutanols undergo ring contraction with complete stereospecificity as shown in the example of equation 164[276].



(164)

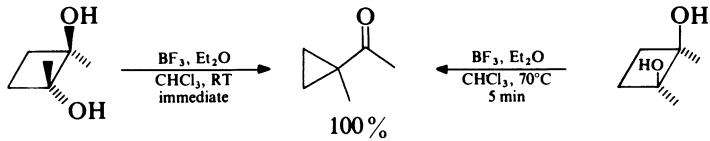
3. 1,2-Cyclobutanediol

Both *cis*- and *trans*-1,2-cyclobutanediols rearrange under the influence of acid to give the corresponding cyclopropanecarboxaldehydes or ketones in high yields (equation 165)[163b,277].



(165)

In the case of 1-alkylated 1,2-cyclobutanediols, the tertiary hydroxyl is the preferred or exclusive leaving group. With 1,2-dialkylated diols, the *trans* isomers were normally found to rearrange somewhat more easily than the *cis* compounds. For instance, *trans*-1,2-dimethyl-1,2-cyclobutanediol (**243**) underwent immediate quantitative ring contraction to (1-methylcyclopropyl) methyl ketone (**244**) upon treatment with boron trifluoride etherate at room temperature while the ring contraction of the *cis* isomer (**245**) was observed only on heating at 70°C for 5 min in the presence of BF_3 and Et_2O (equation 166)[278].



(166)

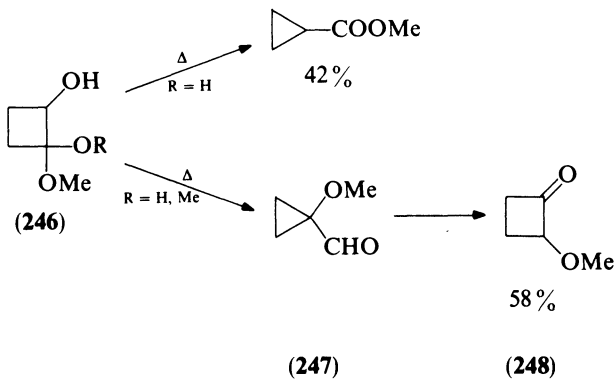
(**243**) (**244**) (**245**)

The 1,2-cyclobutanediols also undergo thermal rearrangement. The reaction is performed in high yields either in a sealed tube at 230–270°C or in the gas phase. The simple mono- and dialkylated compounds give products which are the same as those formed in the acid-catalysed reaction, and the *trans* diols were found to rearrange faster than their *cis* counterparts (equation 166)[278].

Moreover, in the gas phase some *trans* diols were found to undergo quantitative ring contraction at 310°C, whereas the corresponding *cis* isomers remained unchanged at this temperature. On simple distillation at atmospheric pressure, several 1,2-dialkyl *cis*-1,2-cyclobutanediols undergo alkyl migration rather than ring contraction, giving 2,2-dialkylcyclobutanones in high yields[278].

4. 2-Hydroxycyclobutanone hydrate, hemiacetal and acetal

Attempts to effect the contraction of 2-hydroxycyclobutanone by heating in a sealed tube either neat (210°C) or with water (230°C) (presumably the hydrate) apparently fail to give any reaction. In fact, the $C_4 \rightarrow C_3$ ring contraction takes place, but the product is a 1-hydroxycyclopropanecarboxaldehyde which then readily undergoes the reverse $C_3 \rightarrow C_4$ ring expansion (cf. Section III.E)[164]. On the other hand, heating 2-hydroxycyclobutanone in methanol leads to the corresponding hemiacetal (**246**) (R = H), which then is able to undergo a $C_4 \rightarrow C_3$ ring contraction into methyl cyclopropanecarboxylate (42%) and 1-methoxycyclopropanecarboxaldehyde (**247**). The latter undergoes a rapid $C_3 \rightarrow C_4$ ring expansion under these conditions to 2-methoxycyclobutanone (**248**) (58%) (equation 167)[164].

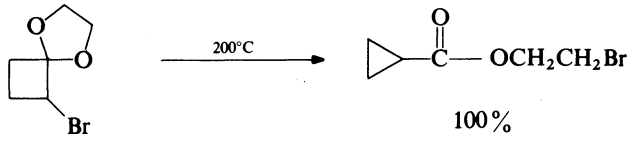


(167)

The corresponding acetal, i.e. 2,2-dimethoxycyclobutanol (**246**) (R = Me) also undergoes thermal rearrangement (220°C) to 1-methoxycyclopropanecarboxaldehyde (**247**) and on further heating, to 2-methoxycyclobutanone (**248**) (equation 167)[164].

5. 2-Bromocyclobutanone acetals

2-Bromocyclobutanone acetals (**249**) are quantitatively converted to cyclopropanecarboxylic esters (**250**) and alkyl bromides, or to bromoesters in the case of cyclic acetals, upon simple heating in a sealed tube at 200°C (equation 168)[279].



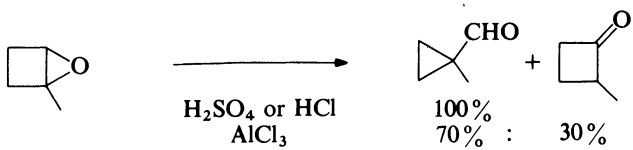
(249) (250) (168)

The stereochemical and kinetic data for the thermal ring contraction which proceeds with inversion of configuration at the halogen-receiving carbon atom are consistent with an intermolecular halogen transfer and exclude the occurrence of a thermally allowed pericyclic reaction[279].

The ambivalent nature of the acetal function is shown by the fact that it acts equally as an electron-withdrawing (equation 167) or an electron-donating (equation 168) substituent.

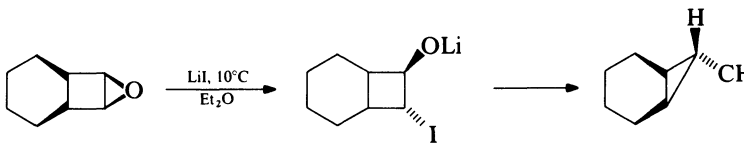
6. Epoxycyclobutane

The first ring contraction of a 1,2-epoxycyclobutane was reported by Criegee and Knoll; however, the conditions used also led to ring-opening products[277a]. Extensive studies have since shown that the careful use of protic acids gives mainly cyclopropyl products (equation 169)[280].



(169)

The use of aluminium chloride leads to some concomitant cyclobutanone formation, when possible. Lithium iodide and lithium thiocyanate have also been used as catalysts, and in these cases the reaction occurs stereospecifically with net retention of configuration at the migration terminus, presumably via the intermediacy of a lithium 2-iodocyclobutoxide (equation 170)[281].

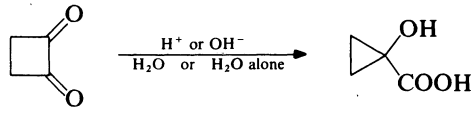


(170)

This ring contraction, which occurs also on simple heating, could be considered as a 2a + 2s pericyclic reaction, thermally allowed[267c].

7. 1,2-Cyclobutanedione

The ring contraction of 1,2-cyclobutanediones was first postulated in order to account for the formation of an α-ketoacid from 2-phenylcyclobutanedione[282], and in the acid- or base-catalysed ring contraction of a 1,2-dichlorocyclobutanecarbonate[283]. It has been shown that 1,2-cyclobutanediones undergo ring contraction to 1-hydroxycyclopropanecarboxylic acids (equation 171).

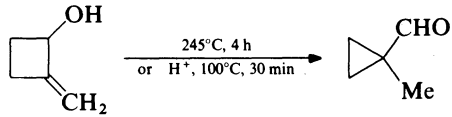


(171)

The reaction may be catalysed by an aqueous acid or base[164,167,284], by methoxide ion and amines or hydrazines[285] and it even takes place although more slowly in pure water or methanol[164,284]. Photochemical ring contractions have also been reported[285a,286].

8. 2-Alkylidenecyclobutanol

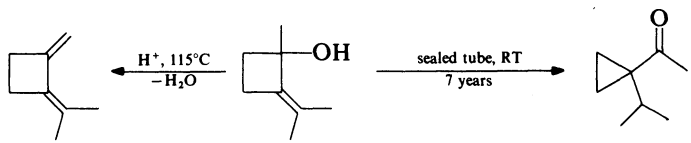
On heating in a sealed tube at 245°C for 4 h or with an acid catalysis (5% aqueous sulphuric acid, 30 min) at 100°C, 2-methylenecyclobutanol (**251**) undergoes quantitative ring contraction to 1-methylcyclopropanecarboxaldehyde (**252**) (equation 172)[164,287].



(172)

(**251**) (**252**)

The reaction does not occur on heating at 310°C for 2 h in the gas phase or in basic medium (e.g., pyridine, aqueous sodium hydroxide) suggesting that the reaction involves the protonation of the double bond. When the hydroxyl group is tertiary, it appears impossible to avoid the competitive dehydration reaction. However, after standing at room temperature for 7 years in a sealed tube, 2-isopropylidene-1-methylcyclobutanol (**253**) has undergone ring contraction to the extent of 60% (equation 173)[164,287].



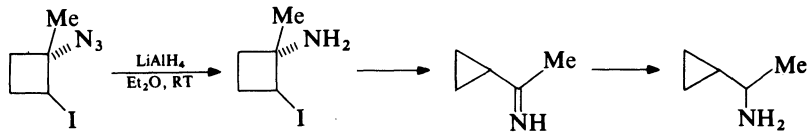
(173)

100% (**253**) 60%

When a γ-hydrogen is present, the ring contraction product undergoes in turn ring-opening into homoallylic aldehyde, by a thermal homo[1.5]hydrogen shift (cf. equation 25)[164,287].

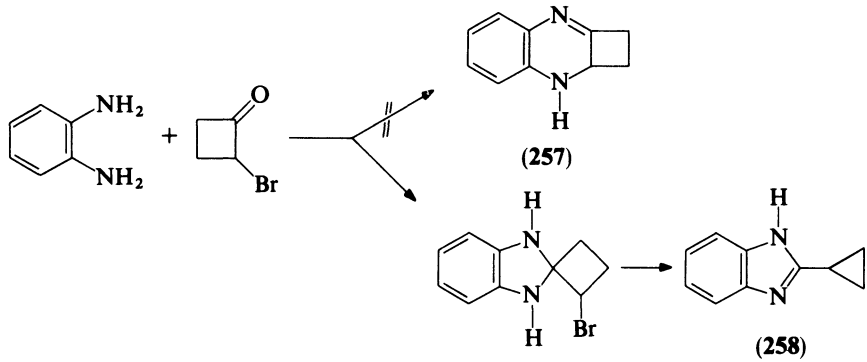
9. 2-Halocyclobutylamine

2-Iodocyclobutyl azides (**254**) have been converted into cyclopropylmethylamines (**256**) by treatment with lithium aluminium hydride, via the intermediacy of the corresponding iodoamines (**255**) (equation 174).



(**254**) (**255**) (**256**) (174)

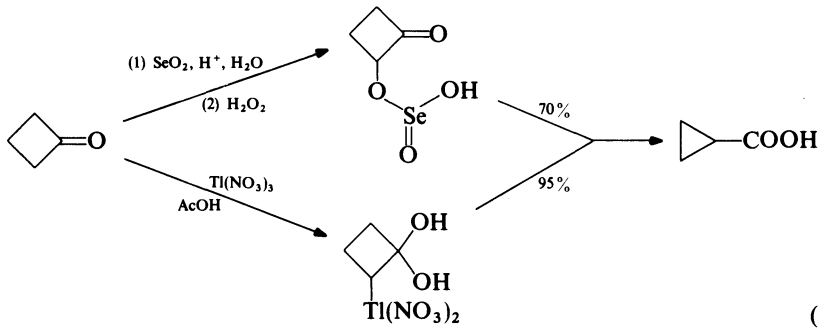
The rearrangement could also be affected by the action of NaN_3–IN_3 on 2-iodocyclobutyl azides (**254**) in acetonitrile[288]. The reaction of *o*-phenylenediamine with 2-bromocyclobutanone does not afford a fused dihydroquinoxaline derivative (**257**) as first claimed[289], but 2-cyclopropylbenzimidazole (**258**) is formed by way of a similar ring contraction (equation 175)[290].



(175)

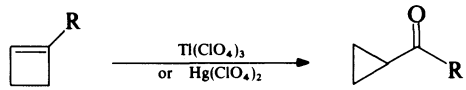
10. Miscellaneous

Treatment of cyclobutanone under aqueous acidic conditions with either hydrogen peroxide/selenium dioxide or thallium(III) salts gives cyclopropanecarboxylic acid in a good yield (equation 176)[141].



(176)

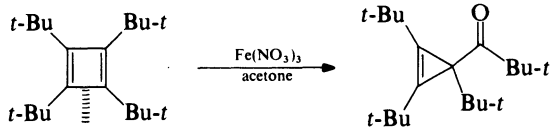
Likewise, cyclobutene and 1-methylcyclobutene undergo mercury(II) and thallium(III) oxidation with ring contraction (equation (177))[291].



(177)

R = H, Me

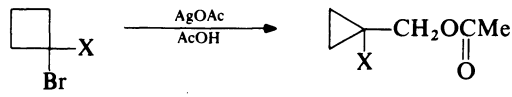
The analogous rearrangement of a cyclobutadiene complex (**259**) has been effected using cerium(IV) or iron(III) reagents (equation 178)[292].



(178)

(259)

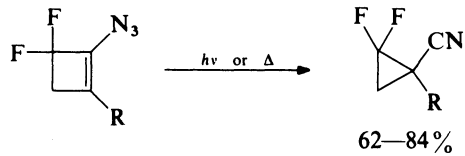
Cyclopropylmethanol derivatives bearing electronegative α-substituents have been prepared from the ring contraction of α-substituted bromocyclobutanes on heating in glacial acetic acid containing an excess of silver acetate (equation 179)[293].



(179)

X = COPh, CO_2Me, $CONH_2$, NO_2

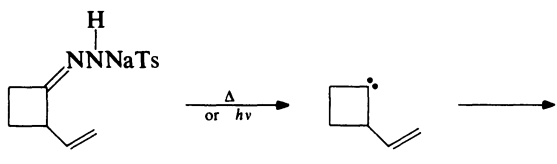
Thermally or photochemically induced ring contraction of 2-azido-3,3-difluorocyclobutenes (**260**) leading to 2,2-difluorocyclopropyl carbonitriles (**261**) in good yields have been obtained on heating at 75–100°C in aprotic solvent or upon irradiation at $\lambda > 290$ nm (equation 180)[294].



(180)

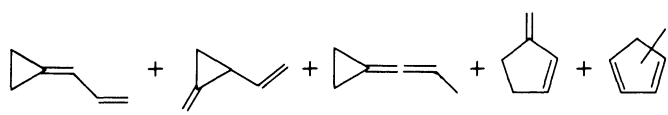
(260) (261)

Ring contraction of cyclobutylidenes is known, but not so widely explored. Thus, pyrolysis (200°C) or irradiation of the lithium[295] or sodium salt[296] of cyclobutanone tosylhydrazone (**262**) gave the 2-vinylcyclobutylidene (**263**) which then rearranged mainly to ring contraction products (equation 181).



(262) (263)

(181)



71% (85.3 : 2.1 : 1.9 : 4.9 : 0.4)

It should be realized that the five-membered ring products stem from the subsequent $C_3 \rightarrow C_5$ ring expansion of the 2-methylenevinylcyclopropane formed by the ring contraction (cf. Section IV.A.1, equation 141).

VI. CONCLUSION

The foregoing sections show that cyclopropyl derivatives constitute very useful building blocks for synthetic purposes. They undergo ring-opening reactions under various conditions, leading fairly often to specific products in high yields.

Adjacent to an electron-deficient centre, a cyclopropane ring undergoes readily a $C_3 \rightarrow C_4$ ring enlargement to a four-membered ring derivative. Furthermore, when an electron-donor substituent is also present on the same carbon as shown in equation 67 the specific rearrangement leads to cyclobutanone derivatives. The latter provide unusually promising intermediates for the versatile elaboration of five-, six- and eight-membered rings. The reaction also leads to the challenging β-lactams.

An efficient three-carbon annelation process is based on the vinylcyclopropane–cyclopentene rearrangement. The occurrence of five-membered rings in an increasing number of natural products of biological importance has recently stimulated the investigation of new methodologies for the construction of the cyclopentane moiety. Among others, the thermal $C_3 \rightarrow C_5$ ring expansion of 1-siloxy-1-vinylcyclopropanes which leads to cyclopentanone silyl enol ethers which are able to undergo further regiospecific alkylation, and the acid-induced $C_3 \rightarrow C_5$ ring expansion of 1-hydroxycyclopropylcarbinol derivatives provide powerful synthetic tools.

In the cyclobutyl systems so far examined which undergo a $C_4 \rightarrow C_3$ ring contraction according to equation 157 the electron-donating substituent A can be a negatively charged oxygen or an hydroxy, acetal, epoxide or amino group with non-bonding electrons. The leaving group X may be an halogen or a tosyloxy group, as well as the oxygen of a carbonyl, hydroxy, acetal or epoxide group indicating the ambivalence of these functions. It can also be the protonated double bond of an α-alkylidene substituent. This $C_4 \rightarrow C_3$ ring contraction of the readily available cyclobutane derivatives, which usually gives a single product in high yield, constitutes not only the reverse rearrangement of the $C_3 \rightarrow C_4$ ring expansion[267c,297] but provides also a convenient pathway to the attractive three-membered ring[298].

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CHAPTER 14

Radiation chemistry and hot atom chemistry of cyclopropane and its derivatives

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I. RADIATION CHEMISTRY OF CYCLOPROPANE

A. Introduction

Radiation chemistry is the study of the chemical effects produced in a system by the absorption of ionizing radiation. This definition includes the chemical effects due to radiation from radioactive sources, high energy charged particles and short wavelength (less than about 400 Å)[1] electromagnetic radiation from accelerators. The principal characteristic of high energy radiation is that it causes ionization in all materials. This makes a distinction between radiation chemistry and photochemistry[2,3]. Photochemistry deals with longer electromagnetic radiation wavelengths which have lower energy (less than about 30 eV). This relatively low energy leads in many cases only to the excitation of the molecules and does not produce ions. Usually, the energy of the particles and photons applied in radiation chemistry is much higher. The whole energy is not absorbed by a single molecule, as in photochemistry, but rather distributed over several molecules, along the track of the ionizing particle or photon. The high energy photons and particles are not selective and may ionize, excite or dissociate any molecule lying in their path.

The high energy photons or particles lose energy in successive events and produce primary electrons which produce several secondary electrons with lower energies[4]. The chemical effects of ionizing radiation occur almost exclusively through the secondary electrons most of which have less than 100 eV. These electrons will cause ionization and excitation of the surrounding molecules and will lose energy until they reach thermal energies. In many solvents these thermal electrons polarize the solvent and are bound in a stable quantum state to it; these electrons are called solvated electrons.

The study of radiation chemistry might be divided, from an experimental point of view, into two parts. The first part is the study of unstable intermediates which have short lifetimes and thus cannot be studied by the usual methods of chemistry. The second part is the study of the final products of the radiolysis which are measured by common chemical techniques.

One way to make the short-lived intermediates amenable to study is to increase their lifetime, usually by irradiating in the solid state and at very low temperatures. Then, the intermediates can be measured at the end of the irradiation by optical absorption spectroscopy or ESR.

Another method of making the lifetime longer in the liquid phase, is by adding compounds which upon addition of radicals produce long-lived radicals; this method is called spin trapping[5].

More common way in the liquid phase is pulse radiolysis[6]. In this technique, electron accelerators which can deliver intense pulses of electrons lasting a very short time (ns up to μs) are used. Each single pulse can produce a concentration of intermediates high enough to be studied by methods such as light absorption spectroscopy or electrical conductivity.

The yields of radiolysis products are always expressed by the *G*-value. The *G*-value is defined as the number of particles (molecules, radicals, ions) produced or consumed per 100 eV of energy absorbed in the system.

The unit used for the absorbed energy (dose) is the rad, defined as 1 rad = 100 erg/g $= 6.243 \times 10^{13}$ eV/g.

B. Initial Processes

Platzman[7,8] in his theory of the initial processes in the radiolysis of chemicals assumed that when a polyatomic molecule AB is receiving energy of radiation, this energy may be utilized in two ways: (*a*) in a direct ionization (equation 1):

$$AB \rightarrow AB^+ + e^- \tag{1}$$

with a probability δ, or (*b*) in the formation of a molecule in a super-excited state (a term introduced by Platzman to indicate a molecule whose energy content is larger than that required for ionization) (equation 2):

$$AB \rightarrow AB^{**} \tag{2}$$

with a probability $(1-\delta)$. This super-excited state can give either preionization or dissociation (equation 3):

$$AB^{**} \longrightarrow \begin{matrix} AB^+ + e^- \\ A + B \end{matrix} \tag{3}$$

Platzman[7] suggested that the probability δ is much less than unity and there is real formation of super-excited states. Hatano[9] calculated the yield of the super-excited molecules and the consequent dissociation (in values of g_d, number of dissociations per 100 eV energy absorbed) for cyclopropane together with some other hydrocarbons. He used the optical approximation introduced by Platzman[8], assuming that the yield g_d is proportional to the square of the dipole-matrix-element M_d^2 calculated from the optical spectra (equation 4).

$$M_d^2 = \int_I^\infty [1-\eta(E)]\frac{R}{E}\frac{df}{dE}dE \tag{4}$$

where E is the excitation energy, R is the Rydberg energy, I is the ionization energy, df/dE is the differential oscillator strength and $\eta(E)$ is the probability of ionization upon excitation at E. There are no available data for W, the energy required for ion–electron pair formation, in cyclopropane and by assuming $W = 23.0$ eV Hatano obtained $g_d = 0.9$ for cyclopropane, a similar value to that found for other hydrocarbons.

C. Radiolysis of Cyclopropane in the Gas Phase

Yang[10] studied the yields of the products in the radiolysis of gaseous cyclopropane, without scavangers and in the presence of nitric oxide which is known to suppress radical processes in homogeneous gas phase reactions[11]. The same yield of hydrogen was found with and without the addition of 10 mol % of NO ($G(H_2) = 1.14$) indicating that H_2 is formed in a non-radical process. This value is much lower than the *G*-values of hydrogen formation in the radiolysis of saturated hydrocarbons which are about 5–8[12,13] and is comparable to the yield of hydrogen formation in the radiolysis of olefins. This observation is possibly due to the weaker C–C bonds and stronger C–H bonds in cyclopropane compared to alkanes (C–H 101 kcal mol^{-1} in cyclopropane compared to 98 in propane; C–C 54 kcal mol^{-1} in cyclopropane compared to 85 kcal mol^{-1} for propane)[14], thus favoring more C–C bond rupture than scission of the C–H bonds, while in alkanes the main primary event is C–H bond dissociation. Besides, the weaker C–H bond strength in alkanes enables the formation of H_2 through a radical mechanism.

$$H + R\text{–}H \rightarrow R + H_2$$

whereas the abstraction of hydrogen from cyclopropane was found to have higher activation energy[15]. Tanaka and coworkers[16] found that $G(H_2)$ in the radiolysis of cyclopropane is scarcely suppressed at all by the addition of electron scavenger such as SF_6 even at high concentration (about 1 mol %) or by the addition of radical scavenger, C_2H_4, in concentration of about 1 mol %. In the gas phase radiolysis of alkanes, a rapid decrease in $G(H_2)$ is observed upon the addition of a small amount of an electron scavenger[12,13]. Thus, Tanaka and coworkers[16] suggested that the primary process of hydrogen formation in the gas phase radiolysis of cyclopropane may be interpreted, similarly to the case of olefins[17,18], in terms of two processes: the molecular detachment of the hydrogen molecule

and the hydrogen atom abstraction of hot hydrogen atoms formed by the direct excitation which may involve super-excitation.

In contrast to Yang's result who found that 10% NO did not reduce the yield of H_2[10] and the result of Tanaka and coworkers[16] that SF_6 scarcely reduced the yield of H_2, von Bunau and Kuhnert[19] observed a decrease of about 40% in the G-value on addition of 4.5% NO (from 1.38 to 0.86) or 6% SF_6 ($G(H_2) = 0.82$). Scala and Ausloos[20a] studied the gas phase photolysis and radiolysis of c-$C_3D_6 + H_2S$ mixtures. They observed that HD formation was several times larger than that of D_2 even in mixtures containing only 10% H_2S where the yield of $D_2 : HD : H_2$ was in the ratio 1 : 4 : 1. This observation indicates that a relatively high yield of deuterium atoms react with H_2S (equation 5)

$$D + H_2S \rightarrow HD + HS \tag{5}$$

and that the major part of hydrogen gas is produced in radical processes in contrast to Yang's and Tanaka's results. Von Bunau and Kuhnert[19] also studied the radiolysis of a ternary mixture of 47.8% c-C_3H_6 + 4.7% c-C_3D_5H + 47.5% c-C_3D_6 and found the hydrogen gas to consist of 53% H_2, 9% HD and 38% D_2, indicating that the major process of hydrogen molecule formation involves two hydrogen atoms from the same molecule and not a radical process. Thus the formation of H_2 is related to the formation of molecules with a lower proportion of hydrogen such as C_2H_2 and C_3H_4, mainly through previous formation of excited ethylene molecules. The sum of the yields of C_2H_2 and C_3H_4 is close to the yield of H_2.

The disagreement with the experiment of $C_3D_6 + H_2S$ can be explained in the following way[19,20]. In the radiolysis of pure cyclopropane the energetic hydrogen atoms mainly add to the cyclopropane molecule, with ring-opening to give propyl radicals (equation 6):

$$H + c\text{-}C_3H_6 \rightarrow C_3H_7 \tag{6}$$

Von Bunau and Kuhnert[19] calculated from the effect of additives that in the gas phase about 95% of the hydrogen atoms formed in the radiolysis produced propyl radicals in this reaction while only 5% of the hydrogen atoms abstract hydrogen to form H_2 and cyclopropyl radicals (equation 7):

$$H + c\text{-}C_3H_6 \rightarrow H_2 + \dot{C}_3H_5 \tag{7}$$

The high proportion of HD in the case of C_3D_6 + 10% H_2S is explained by the fact that in the presence of H_2S reaction 5 replaces reactions 6 and 7, leading to a radical pathway for H_2 formation which is a very minor one in the case of pure cyclopropane.

A question which does not have any answer is the difference between the various studies[10,16,19] concerning the effect of additives on H_2 yield.

Yang[10] found that in the radiolysis of pure cyclopropane in the gas phase the concentration of ethylene seems to reach a steady state value but when nitric oxide is present the concentration of C_2H_4 increases linearly with the energy absorbed. This is probably due to disappearance of C_2H_4 by reactions with the radicals formed in the system, reactions which are inhibited by the reaction of these radicals with NO. Similarly, in the radiolysis of pure cyclopropane ethane is produced with a yield more than linear with the energy while when NO is present no C_2H_6 is formed.

Tanaka and coworkers[16] found that addition of small amounts of alkanes (C_2H_6, n-C_4H_{10}, n-C_5H_{12}, n-C_6H_{14} and c-C_6H_{12}) increases considerably, by a factor of two, the yield of propane formation in the radiolysis of cyclopropane. This cannot be explained only by the formation of propane from the propyl radical through disproportionation since the increase in propene formation is considerably less than the increase in propane formation. Since the same phenomenon occurs for different alkanes, it cannot be explained either in terms of the direct radiolysis of the additive hydrocarbon or in terms of simple charge transfer processes from cyclopropane to the additive. Using fully deuterated

alkanes as additives Tanaka and coworkers observed that C_3H_7D is formed twice as much as $C_3H_6D_2$. They explained the formation of both species by transfer reactions of H^- and H_2^-, where the former transfer is twice as important as the latter. Both reactions have been observed in a mass spectrometer experiment[21].

Derai and Danon[22] studied the simulated radiolysis of cyclopropane in the gas phase with low energy electrons (6.0–8.0 eV). Table 1 gives the yield of the various products.

TABLE 1. Yields of the various products formed in low energy electron radiolysis of cyclopropane

	Electron energy (eV)			
Product	6.5	7.0	7.5	8.0
C_3H_4 (allene)	0.04	0.08	0.12	0.16
H_2	0.16	0.26	0.22	0.16
C_2H_4	0.12	0.22	0.24	0.28
C_2H_2	0.04	0.16	0.06	0
CH_4	0.04	0.06	0.02	0
C_4H_8[a]	0.10	0.16	0.08	0

[a] Several isomers.

They suggested that the mechanism for low energy electron radiolysis is by formation of triplet cyclopropane which later isomerizes or decomposes (equations 8 and 9).

Primary processes

$$\text{Triplet } c\text{-}C_3H_6 \longrightarrow \begin{cases} \longrightarrow {}^3C_3H_6^* & \Delta H = 0.4 \text{ eV} \\ \longrightarrow \dot{C}_3H_5 + H & \Delta H = 3.8 \text{ eV} \\ \longrightarrow \dot{C}_2H_3 + \dot{C}H_3 & \Delta H = 4.0 \text{ eV} \end{cases} \quad (8)$$

Secondary reactions

$$\begin{aligned} \dot{C}H_3 + \dot{C}_2H_3 &\longrightarrow CH_4 + C_2H_2 \\ \dot{C}_2H_3 + \dot{C}_2H_3 &\longrightarrow C_2H_4 + C_2H_2 \\ \dot{C}_3H_5 + \dot{C}H_3 &\longrightarrow 1\text{–}C_4H_8 \\ \dot{C}_3H_5 + \dot{C}_3H_5 &\longrightarrow C_6H_{10} \\ \dot{C}_3H_5 + \dot{C}_3H_5 &\longrightarrow C_3H_6 + C_3H_4 \end{aligned} \quad (9)$$

$$H + H \xrightarrow{\text{walls}} H_2$$

$$\dot{C}_3H_5 + H \xrightarrow{\text{walls}} C_3H_6$$

Table 2 gives the yields of the various products in ^{60}Co radiolysis of gaseous cyclopropane obtained by the several workers. It shows a good agreement of the yields of the main products obtained in the various studies. However, there are some disagreements, e.g. for propane or isobutane formation. The controversy concerning the *G*-value for propane formation can be explained if von Bunau and Kuhnert's system included small amounts of alkanes which were found to increase the yield of propane from 0.5 to 1.0.

TABLE 2. *G*-values for the various products of gaseous phase radiolysis of cyclopropane

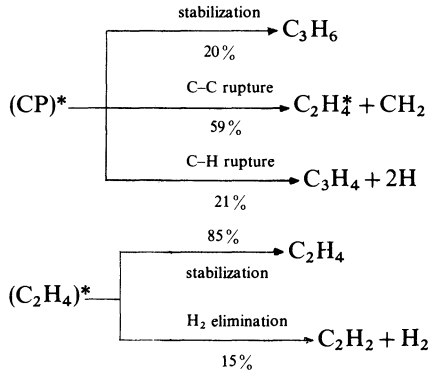
Product	Scala and Ausloos[20b] 1.33 kPa	von Bunau and Kuhnert[19] 60 kPa	Tanaka and coworkers[16] 100 kPa
H_2		1.38	1.36
CH_4		0.16	0.38
C_2H_2	1.04	0.72	—
C_2H_4	3.45	3.28	2.40
C_2H_6	0.65	0.35	—
C_3H_4 (methyl acetylene)		0.20	
C_3H_4 (allene)	0.38	0.37	—
C_3H_8		1.05	0.52
C_4H_8 (several isomers)		0.59	
n-C_4H_{10}		0.39	0.37
i-C_4H_{10}		0.27	0.03
Pentanes		0.42	
Propene	1.0		0.27
trans-2-Butene or isopentane			0.14
Methylcyclopropane			0.18
n-Pentane			0.10
Allylene			0.03
1-Pentene			0.03
2,3-Dimethylbutane or 2-Methylpentane			0.13
3-Methylpentane			0.06
n-Hexane			0.03
C_6 (others)			0.07

Von Bunau and Kuhnert[19] studied the γ-radiolysis of cyclopropane both in direct radiolysis and in Kr- and Xe-sensitized radiolysis. The sensitized radiolysis was studied earlier by Smith and coworkers[23] who showed that the addition of a rare gas increases the percent of cyclopropane consumed for constant irradiation time. The sensitization increases with increasing pressure of the rare gas for constant pressure of cyclopropane. The degree of rare gas sensitization was found, as expected, to be in the order of its energy absorption characteristics (electron density), i.e. Xe > Kr > Ar. Von Bunau and Kuhnert studied the effect of electron scavenger (SF_6) and radical scavenger (NO) on the yield of the various products in direct radiolysis and in the sensitized radiolysis. They explained the different effects of the additives in the three systems by assuming the formation of two reactive species, an excited cyclopropane molecule and an excited cyclopropane ion, whose yields are different in the three systems as can be seen in Table 3.

TABLE 3. Yields of the primary reactive species in the radiolysis of cyclopropane (CP)

	G-Values	
Method of radiolysis	(CP)*	$(CP^{\perp})^*$
Direct	2.5	2.3
Kr-sensitized	1.3	3.0
Xe-sensitized	1.3	3.9

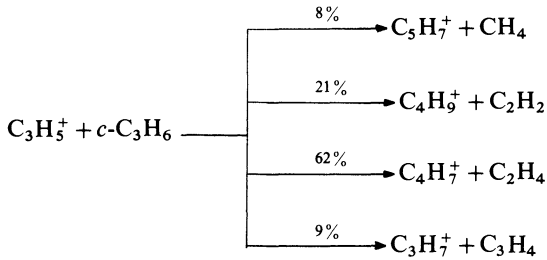
They suggested that the excited cyclopropane can react in three different reactions (equation 10):



(10)

The hydrogen atoms and the carbene formed react further with other molecules of cyclopropane.

The excited cyclopropane ion is either collisionally stabilized to $C_3H_6^+$ or decomposed to give $C_3H_5^+$, $C_3H_4^+$, $C_3H_3^+$ and $C_2H_3^+$ [24]. However, the proportion of these different ions depends on the excitation energy of the $(CP^+)^*$ and consequently is different for the three methods of radiolysis. These ions react with another molecule of cyclopropane, according to equation (11):



(11)

In the case of Kr-sensitization radiolysis products are formed with rates that are significantly lower than in direct and Xe-sensitized radiolysis. This is ascribed to higher yield of the unreactive $C_3H_3^+$ ions by charge transfer from Kr^+ to cyclopropane molecules, while Xe^+ ions generate mainly $C_3H_6^+$, $C_3H_5^+$ and $C_2H_3^+$.

Von Bunau and Kuhnert[19] found that the amount of cyclopropane consumed in the gas phase ($G(\text{-}c\text{-}C_3H_6) = 16.3$) is more than twice the yield of the C_1–C_6 compounds measured ($G = 7.4$). The difference is attributed to the formation of a polymer product.

Holroyd[25] studied the type of the radicals formed in irradiated cyclopropane with the $^{14}C_2H_5$ radical sampling technique and found several intermediates besides the cyclopropyl radical. Not all the hydrocarbons formed were identified but it was found that cyclopropyl and allyl radicals were both present in approximately a 1:1 ratio, indicating that ring-opening is a major process in cyclopropane. The extent of ring-opening decreases for cyclobutane and decreases further for cyclopentane. Similar results that the probability of C–C bond rupture falls from cyclopropane to cyclohexane were observed in the radiolysis of liquid cycloalkanes in an ESR study[26].

D. Radiolysis of Cyclopropane in the Liquid Phase

The radiolysis of liquid phase cyclopropane was studied by Horvath and Foldiak[27] at 30–35 °C under pressure and by Zhitneva and coworkers[28] at −78 °C. The results are summarized in Table 4.

TABLE 4. Yield of products in *G*-values from γ-radiolysis of liquid cyclopropane

Product	30–35 °C Horvath and Foldiak[27]	−78 °C Zhitneva and coworkers[28]
Hydrogen	0.91	1.1
Methane	0.22	0.2
Ethane	0.12	0.2
Ethylene	1.50	1.6
Acetylene	0.32	—
Propane	0.27	0.2
Propene	0.70	0.9
Allene	0.25	—
Methylcyclopropane	0.08	1.4
1-Butene + 1,3-Butadiene	0.13	
cis- and *trans*-2-Butene	0.53	

Horvath and Foldiak suggested the following mechanism (equations 12 and 13):

$$c\text{-}C_3H_6 \rightsquigarrow \begin{cases} c\text{-}C_3H_6^+ + e^- \\ c\text{-}C_3H_6^* \end{cases} \tag{12}$$

$$c\text{-}C_3H_6^+ + c\text{-}C_3H_6 \rightsquigarrow \begin{cases} \dot{C}_3H_7^+ + \dot{C}_3H_5 \\ \dot{C}_4H_7^+ + \dot{C}_2H_5 \end{cases} \tag{13}$$

The radicals formed combine, disproportionate or abstract an hydrogen atom; the ions abstract a hydride ion (equations 14–16):

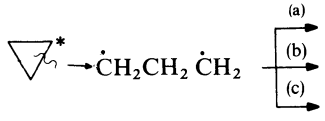
$$\dot{C}_2H_5 \xrightarrow{+H} C_2H_6 \tag{14}$$

$$\dot{C}_3H_5 \xrightarrow{+H} C_3H_6 \tag{15}$$

$$\dot{C}_3H_7^+ \xrightarrow{+H^-} C_3H_8 \; G \text{ (propane)} = 0.27 \tag{16}$$

The decomposition of the excited cyclopropane molecule is suggested to occur either through (1) a one C–C bond rupture (equation 17) or (2) via simultaneous rupture of two C–C bonds (equations 18–22). The relative high yield of C_2 products supports the suggestion of simultaneous rupture of two C–C bonds, i.e. that both ruptures occur before thermalization of the molecule.

(1) *One C–C bond rupture*

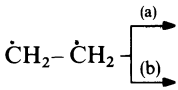


$$\nabla^{*} \rightarrow \dot{C}H_2CH_2\dot{C}H_2 \quad \begin{cases} \xrightarrow{(a)} \nabla \\ \xrightarrow{(b)} CH_3{-}CH{=}CH_2 \; G \text{ (propene)} = 0.7 \\ \xrightarrow{(c)} CH_2{=}C{=}CH_2 + 2H\cdot \text{ (or } H_2) \; G \text{ (allene)} = 0.25. \end{cases} \tag{17}$$

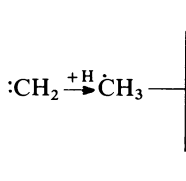
Propene is formed both in reactions 15 and 17b; the sum of the yields is 0.7.

(2) *Two C–C bond rupture*

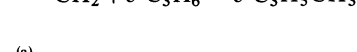
$$\nabla \rightarrow \dot{C}H_2{-}\dot{C}H_2 + {:}CH_2 \tag{18}$$



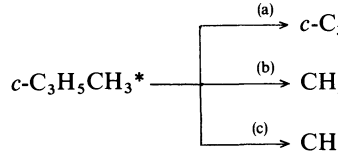
$$\dot{C}H_2{-}\dot{C}H_2 \quad \begin{cases} \xrightarrow{(a)} CH_2{=}CH_2 & G \text{ (ethylene)} = 1.5 \\ \xrightarrow{(b)} CH{\equiv}CH + 2H\cdot \text{ (or } H_2) & G \text{ (acetylene)} = 0.32 \end{cases} \tag{19}$$



$${:}CH_2 \xrightarrow{+H} \dot{C}H_3 \quad \begin{cases} \xrightarrow[(a)]{+H} CH_4 & G \text{ (methane)} = 0.22 \\ \xrightarrow[(b)]{+CH_3} C_2H_6 & G \text{ (ethane)} = 0.12 \end{cases} \tag{20}$$



$${:}CH_2 + c\text{-}C_3H_6 \rightarrow c\text{-}C_3H_5CH_3 \tag{21}$$



$$c\text{-}C_3H_5CH_3^{*} \quad \begin{cases} \xrightarrow{(a)} c\text{-}C_3H_5CH_3 & G \text{ (methyl cyclopropane)} = 0.08 \\ \xrightarrow{(b)} CH_2{=}CHCH_2CH_3 & G \text{ (1-butene)} = 0.13 \\ \xrightarrow{(c)} CH_3CH{=}CHCH_3 & G \text{ (2-butene)} = 0.53 \end{cases} \tag{22}$$

Comparison of the yield of ethylene to acetylene shows that the dimethylene diradical has a probability to be stabilized by intramolecular formation of a C=C bond to produce ethylene five times larger than the probability to split off two hydrogen atoms.

The sum of the yields of the reaction of the carbene diradical, $:CH_2$, 1.20 (equations 20, 22) is lower than the yield of the dimethylene diradical, 1.82. The difference of 0.62 is probably accounted for by the formation of higher molecular weight product. Horvath and Foldiak[27] calculated this difference to be 0.74 but they used G (ethane) as the G-value for the carbene reacting via equation 20b while the suggested mechanism shows that two carbenes are used in this reaction.

This mechanism suggests the formation of hydrogen gas by reactions 17c and 19b. However, the sum of their yields ($0.32 + 0.25 = 0.57$) is lower than the observed yield of hydrogen gas (0.91). This is a different situation than in the gas phase where the yields of $C_2H_2 + C_3H_4$ correlate with the yield of hydrogen. The discrepancy between the two values mentioned by Horvath and Foldiak[27] did not give the true discrepancy. According to their mechanism hydrogen atoms are consumed also in reactions 20 which increase the discrepancy from 0.34 to 0.68. A similar problem exists by summing the yield of all the carbon atoms and H_2 moieties in the product molecules observed by Horvath and Foldiak. This leads to G (C) = 10.72 and $G(H_2) = 11.54$ or 11.67, depending on if one takes

1-butene + 1,3-butadiene to be entirely 1,3-butadiene or entirely 1-butene. In cyclopropane the ratio $C:H_2$ is 1:1, and consequently there is a surplus of hydrogen in the product. This difference was suggested to indicate the occurrence of reactions 23–25:

$$c\text{-}C_3H_6^* \rightarrow c\text{-}\dot{C}_3H_5 + H^* \tag{23}$$

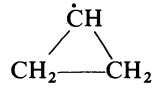
$$H^* + c\text{-}C_3H_6 \rightarrow H_2 + c\text{-}\dot{C}_3H_5 \tag{24}$$

$$2\ c\text{-}\dot{C}_3H_5 \begin{cases} \rightarrow c\text{-}C_3H_4 + c\text{-}C_3H_6 \\ \rightarrow (c\text{-}C_3H_5)_2 \end{cases} \tag{25}$$

However, the authors did not observe in their system cyclopropene or C_6 hydrocarbon, but since cyclopropene is unstable[29,30] it may have polymerized to an unsaturated polymer.

E. Radiolysis of Solid Cyclopropane

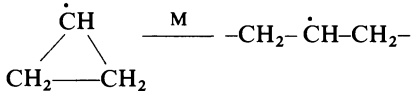
Miyazaki and coworkers[31] studied the ESR spectrum of γ-irradiated pure cyclopropane at 77 K and observed the spectrum of $c\text{-}C_3H_5$ radicals[26]. When cyclopropane containing a small amount of ethane was irradiated at 77 K, a typical spectrum of ethyl radical was observed with higher intensity than that of $c\text{-}\dot{C}_3H_5$, due to hydrogen abstraction from ethane by the excited cyclopropyl radical. Trofimov and coworkers[32] studied the ESR spectrum of irradiated hydrate of cyclopropane at 77 K. A spectrum of five well resolved doublets, belonging to **1** was observed, in addition to the spectrum of H atom.



(1)

No other radicals were formed in this system nor do they appear when the samples were heated. This ESR spectrum is different from that obtained by Miyazaki and coworkers for pure cyclopropane[26] but since both groups claim that their spectrum is of the cyclopropyl radical, at least one of them has a wrong assignment. Trofimov and coworkers also studied the ESR spectrum of irradiated pure cyclopropane at 77 K[32] and their spectrum resembles very much that of Miyazaki and coworkers. This spectrum is more complex than that found for the radiolysis of the hydrate of cyclopropane.

For the irradiated hydrate of cyclopropane at 77 K the intensity ratio of the lines in the spectrum differs slightly from the binomial; however at 153 K it is already close to binomial. When the temperature is further increased there are no changes in the spectrum up to complete recombination of the radicals at 262 K. When pure cyclopropane was heated to 113 K the lines of the cyclopropyl radical (**1**) disappeared and the intensity of the lines of another radical (**2**) increased. At 77 K both radicals **1** and **2** are present but around 113 K all radicals **1** are converted to radicals **2**. The most probable structure of **2** is given in equation 26; the end groups are bound to other molecules of cyclopropane.



(1) **(2)** (26)

M can be a cyclopropane but not water molecules, since formation of radical **2** was not observed in the irradiated hydrate of cyclopropane.

At higher temperatures (ca. 138 K) radicals **2** disappear and lines of another radical appear. The new radical disappears by recombination at 143 K. The structure **3** was suggested for this radical without further details.

$$-CH_2CH\cdots\dot{C}H\cdots CHCH_2-$$

(3)

F. Comparison of Cyclopropane with Other Hydrocarbons

Liquid phase radiolysis of straight chain hydrocarbons C_3–C_7 give similar yields of H_2 formation for all the hydrocarbons, $G = 4.95 \pm 0.15$, and of C–C bond rupture, $G = 1.50 \pm 0.25$[33]. For cycloalkanes the radiolysis yields are different, $G(H_2)$ is a monotonous increasing function of the molecular weight and G(C–C rupture) is a decreasing function. There are no large differences from C_5 to C_{10} and from C_3 to C_4 and the main differences are between these two groups. The $G(H_2)$ values for cyclopropane and cyclobutane are much lower than those for the other cycloalkanes (5.6 ± 0.3) which are close to the value of the straight chain alkanes. The yields of H_2 are close to those characteristics of *n*-alkenes (propene 0.8, 1-butene 0.73). Foldiak[33] explained this as due to the stronger C–H bonds in cyclopropane and in cyclobutane. However the C–H bond strength is not so different: (100.7 kcal mol^{-1} in cyclopropane, 96.5 kcal mol^{-1} in cyclobutane, 95.5 kcal mol^{-1} in cyclohexane and 98 kcal mol^{-1} in ethane)[13]. It seems that the right correlation is with the C–C bond strength which differs substantially for cyclopropane (53.5 kcal mol^{-1}) than for cyclohexane (84.5 kcal mol^{-1}). This correlation also fits the fact that for branched alkanes where there are weaker C–C bonds and weaker C–H bonds, G (C–C) increases and $G(H_2)$ decreases compared to the straight chain hydrocarbons. In the latter the main product of radiolysis is hydrogen in spite of the C–H bond being stronger by about 10 kcal mol^{-1} than the C–C bond. This observation has been explained by the 'exciton energy' which assumes that a part of the energy localized at the C–H bonds does not participate in intramolecular transfer processes. The lower the C–C bond strength the higher the probability that sufficient energy to break the C–C bond is transferred from the C–H bonds. Foldiak[33] showed that for a constant number of carbon atoms G(C–C) in various alkanes is a decreasing function of the C–C dissociation energy. He plotted the G(C–C) per C–C bond in the molecule as a function of the strain energy (Figure 1). The clear difference between the C_3–C_5 hydrocarbons (where the specific G(C–C) values decrease with decreasing strain energy) and the cycloalkanes higher than C_6 (for which the specific G(C–C) decreases with increasing strain energy) was ascribed to the different nature of strain energy in small rings (C_3–C_5) and in large rings ($> C_6$). For cycles smaller than C_5 the strain is due mainly to the distortion of the C–C–C bond angles from the 'normal' tetrahedral ones. In cycles higher than C_6 van der Waals repulsion between non-bonded crowded hydrogen atoms becomes higher, thus increasing the probability of C–H bond rupture and consequently decreasing the yield of C–C bond rupture.

It seems a bad practice to use the specific G(C–C) (G(C–C) divided by the number of C–C bonds in the molecule) for the plot. Assuming the C–H and C–C bonds strengths are independent of the cycle size we will expect G(C–C) to be the same for all the cyclic molecules but in a plot of the specific G(C–C) it will decrease with increasing number of carbon atoms in the molecule due to the larger number of C–C bonds. The large difference between the C_3–C_6 hydrocarbons and the larger cycles is seen even better if G(C–C) is plotted instead of the specific G(C–C) although instead of the decrease from C_3 to C_4 it should show an increase. This is probably the reason why Foldiak plots the specific G(C–C).

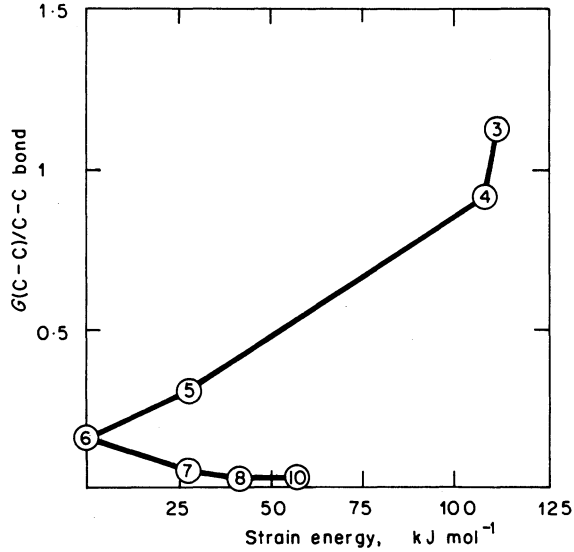


FIGURE 1. The specific G(C–C) values of cycloalkanes as a function of the strain energy. The numbers in circles denote the numbers of carbon atoms in the rings. (Taken from Foldiak[33] with the permission of the author)

The free ion yield in the radiolysis of cyclopropane at $-90\,^{\circ}C$ is very low and is not more than $G = 0.04$[34]. The electrons formed are scavenged by N_2O with efficiency considerably lower than for ethane or propane although higher than for propene and ethylene[35], suggesting a rather short time for ion–electron neutralization. The low free ion yield is in contrast with some hydrocarbons having similar degree of symmetry and sphericity, e.g. neopentane, neohexane and isooctane which give high yields of free electron. In its low free yield and low efficiency for reaction with electron scavenger, cyclopropane is also closer to alkenes than to alkanes. The low free ion yield might be due to the short electron–ion separation caused by the efficient energy transfer from the electrons formed by the radiolysis to the molecules[35].

G. Radiolysis of Cyclopropane Derivatives

Foldiak and his coworkers[36,37] studied the radiolysis of liquid butyl cycloalkanes. In the radiolysis of alkylcyclohexanes[38] the major C–C bond rupture is dealkylation of the side chain. The dealkylation is also an important pathway in the radiolysis of alkylbenzene[39] although only for butylbenzene it was found to be the major C–C bond rupture. In the radiolysis of butylcyclobutanes[40] the dealkylation and the skeletal rearrangement are of minor importance and the main C–C bond ruptures are in the ring leading to ethylene and a C_6 alkene. This most abundant process of cleavage of two C–C bonds was ascribed to the exceptionally high value of ring strain of four-membered rings. Four different isomers of butylcyclopropane were studied: *n*-butylcyclopropane, isobutylcyclopropane, *s*-butyl cyclopropane and *t*-butylcyclopropane. The radiolysis of the pure compounds and the compound saturated with O_2 to scavenge radicals were studied. The main product for each

isomer is ethylene formed by the simultaneous rupture of two C–C bonds adjacent to the tertiary C atom of the ring. Other important products are pentenes and hexanes. The pentenes are formed as a complimentary part to ethylene (equation 27):

$$\xrightarrow{\sim\sim} \dot{C}H_2\,\dot{C}H_2 + :CHCH_2CH_2CH_2CH_3 \qquad (27)$$

$$CH_2{=}CH_2 \qquad CH_2{=}CHCH_2CH_2CH_3$$

The hexenes can be formed by the rupture of two C–C bonds, one of them not adjacent to the tertiary C atom of the ring yielding a carbene (equation 28):

$$\xrightarrow{\sim\sim} :CH_2 + \dot{C}H_2\,\dot{C}HCH_2CH_2CH_2CH_3$$

$$CH_2{=}CHCH_2CH_2CH_2CH_3 \qquad (28)$$

$$\xrightarrow{\sim\sim} :CH_2 + \dot{C}H_2\,\dot{C}HCHCH_2CH_3$$

$$CH_2{=}CHCHCH_2CH_3$$

The carbene contributes to the formation of methane and of other molecules by addition to several reaction products. The yield of ethylene is influenced very little by the presence of oxygen indicating that a unimolecular process leads to its formation. The ring-opening is much more extensive in alkylcyclopropane than in alkylcyclohexane since in alkylcyclohexane the weakest C–C bond is between the ring and the side chain, while in the alkylcyclopropane the C–C bond in the ring is considerably weaker than that connecting the ring to the side chain. The yield of ethylene differs considerably for the four isomers (Table 5). Table 5 shows that the decomposition increases when the carbon atom attached to the ring changes from primary to secondary and to tertiary.

The yield of ethylene is exceptionally high for *s*-butylcyclopropane. Foldiak and coworkers[36,37] explained it as due to its formation not only from a simultaneous cleavage of two bonds of the ring but also from an ethyl radical which is detached from the tertiary carbon atom in the side chain. A support to this suggestion is the observation of formation of higher yield of ethane. However, this correlation can hold only if these ethyl radicals are excited since otherwise the amount of ethylene produced in this way should equal that of the ethane and the small difference in ethane yield is not sufficient to explain the larger difference in the yields of ethylene. Moreover, since for ethyl radical the ratio of disproportionation/combination is about 1, the yield of ethylene from ethyl radicals should be equal to the yield of butane which is only 0.12.

The most conclusive evidence that the larger yield of ethylene from *s*-butylcyclopropane is not due to the ethyl radicals is that the difference still exists in the presence of scavenger radicals as O_2. In the presence of oxygen the yield of ethylene is $G = 0.30$, 0.20, 1.00, and 0.53 for *n*-butyl, isobutyl, *s*-butyl and *t*-butyl, respectively.

TABLE 5. The yields (*G*-values) of the various products in the radiolysis of pure liquid butylcyclopropane isomers C_3H_5R[36]

Product \ R	*n*-Butyl	Isobutyl	*s*-Butyl	*t*-Butyl
Methane	0.10	0.20	0.15	0.25
Ethane	trace	trace	0.30	0.09
Ethylene	0.56	0.39	1.20	0.62
Propane	0.07	0.08	0.03	0.26
Cyclopropane	0.01	0.01	0.02	0.05
Propene	0.12	0.22	0.14	0.20
Butanes	0.06	0.07	0.12	0.08
Butenes	0.15	0.19	0.13	0.28
Pentanes	0.02	—	0.02	0.09
Pentenes	0.33	0.29	0.10	0.02
Hexanes	0.02	0.05	0.02	0.36
Hexenes	0.51	0.57	0.31	0.62
Alkylcyclopropane[a]	0.05	—	0.20	—
C_7 hydrocarbons	0.30	0.21	0.20	0.61
Total	2.30	2.30	2.94	3.53
Total in the presence of O_2	1.51	1.51	1.73	2.81

[a] In the case of R = *n*-butyl it is ethylcyclopropane, in the case of R = *s*-butyl it is the sum of equal yields of ethyl- and isopropyl cyclopropane.

For all four isomers the yield of dealkylation is low, not higher than $G = 0.05$, a value even lower than that found with butylcyclobutanes and far lower than that for the higher cycloalkanes ($G \geqslant 0.2$).

The yield of C_7 products, which might be indicative of isomerization processes via one C–C bond cleavage in the ring, is about the same as that of C_8 products formed in the radiolysis of cyclobutane (10–20%). However the effect of oxygen is small for three of the four isomers of butylcyclopropane (except in the case of the *s*-butyl isomer) while for butylcyclobutane the effect is more pronounced, probably indicating that for the cyclopropane the monomolecular isomerization proceeds with a higher probability than in the radiolysis of four-membered rings.

H. Radiolysis of Mixtures Containing Cyclopropane

Smith and coworkers[2,3] studied the radiolysis of mixtures of cyclopropane and hydrogen sensitized by rare gases. They found that the addition of krypton increased the percent of cyclopropane consumed for constant irradiation time and the sensitization increases with increasing pressure of krypton. The degree of rare gas sensitization is in the order of their energy absorption characteristics Xe > Kr > Ar. They found that when hydrogen was added to a constant composition radiolysis system of rare gas and cyclopropane the rate of disappearance of cyclopropane is retarded; the initial rate of disappearance is linear with the reciprocal pressure of hydrogen, $p_{H_2}^{-1}$. Although no new products were formed when H_2 was present, the ratio of saturated to unsaturated products increased with increasing H_2 pressure. A material balance showed that a large amount of polymerization to higher molecular weight product must have occurred in the system cyclopropane + H_2 + Ar. The yields of the main products followed the order propane

> *n*-butane > isobutane > ethane > propylene > ethylene > methylcyclopropane > 2-methyl pentane > *n*-pentane.

The kinetics of the system were analyzed by the reactions of equations 29–35:

$$\mathrm{Ar} \longrightarrow \mathrm{Ar^+ + e^-} \tag{29}$$

$$\mathrm{H_2} \longrightarrow \mathrm{H_2^+ + e^-} \tag{30}$$

$$c\text{-}\mathrm{C_3H_6} \longrightarrow \text{disappearance of } \mathrm{C_3H_6} \tag{31}$$

$$\mathrm{Ar^+} + c\text{-}\mathrm{C_3H_6} \xrightarrow{k_{32}} \text{disappearance of } \mathrm{C_3H_6} \tag{32}$$

$$\mathrm{H_2^+} + c\text{-}\mathrm{C_3H_6} \xrightarrow{k_{33}} \text{disappearance of } \mathrm{C_3H_6} \tag{33}$$

$$\mathrm{Ar^+ + H_2} \xrightarrow{k_{34}} \mathrm{ArH^+ + H} \xrightarrow{\mathrm{e^-}} \mathrm{Ar + 2H} \tag{34}$$

$$\mathrm{H_2^+ + H_2} \xrightarrow{k_{35}} \mathrm{H_3^+ + H} \xrightarrow{\mathrm{e^-}} \mathrm{H_2 + 2H} \tag{35}$$

The analysis yields equation 36 for the initial rate of disappearance of cyclopropane:

$$\left(\frac{-\mathrm{d}[\mathrm{C_3H_6}]}{\mathrm{d}t}\right)_{t=0} = a + \frac{b}{1+c_1[\mathrm{H_2}]} + \frac{d[\mathrm{H_2}]}{1+c_2[\mathrm{H_2}]} \tag{36}$$

where

$$a = \frac{Q_{\mathrm{C_3H_6}} \cdot [\mathrm{C_3H_6}] \cdot G(-\mathrm{C_3H_6})}{100}$$

$$b = \frac{Q_{\mathrm{Ar}}[\mathrm{Ar}]}{W_{\mathrm{Ar}}}$$

$$c_1 = \frac{k_{34}}{k_{32}[\mathrm{C_3H_6}]}$$

$$c_2 = \frac{k_{35}}{k_{33}[\mathrm{C_3H_6}]}$$

$$d = \frac{Q_{\mathrm{H_2}}}{W_{\mathrm{H_2}}}$$

and

Q_i = the rate of absorption of energy by the ith component at unit concentration;
$G(\mathrm{C_3H_6})$ = the 100 eV yield for the disappearance of cyclopropane in the radiolysis of pure cyclopropane;
W_i = average energy expended in forming an ion-pair in component i.

The only variable is equation 36 is $[\mathrm{H_2}]$ since $[\mathrm{C_3H_6}]$, [Ar] and the radiation intensity are kept constant. The quantities b, d, and $Q_{\mathrm{C_3H_6}}$ can be determined independently from dosimetry experiments. The linearity of the initial rate of c-$\mathrm{C_3H_6}$ disappearance with the reciprocal pressure of $\mathrm{H_2}$ will fit equation 36 if $c_i[\mathrm{H_2}] \gg 1$ (cf. equation 37):

$$\left(\frac{-\mathrm{d}[\mathrm{C_3H_6}]}{\mathrm{d}t}\right)_{t=0} = \left(a + \frac{d}{c_2}\right) + \frac{b}{c_1} \cdot \frac{1}{[\mathrm{H_2}]} \tag{37}$$

Thus the initial slope when $[H_2]^{-1} \to 0$ equals b/c_1 and the intercept of the linear plot on the rate of disappearance axis is equal to $a + (d/c_2)$. Since b and d are determined from dosimetry experiments an additional relationship is required to determine all the parameters. This is obtained from the rate of disappearance using very small amounts of hydrogen (equation 38):

$$\lim_{[H_2]\to 0}\left(\frac{-d[C_3H_6]}{dt}\right)_{t=0} = a + b \tag{38}$$

The following rate constant ratios were obtained:

$$\frac{k_{34}}{k_{32}} = 4.2; \qquad \frac{k_{35}}{k_{33}} = 0.15$$

Using known values of k_{34} and k_{35} they obtained:

$$k_{32} = 2.7 \times 10^{11}\ \text{mol}^{-1}\,\text{s}^{-1}$$
$$k_{33} = 8.4 \times 10^{12}\ \text{mol}^{-1}\,\text{s}^{-1}$$

The much higher efficiency of hydrogen compared to argon cannot be explained by the usual ion-molecule reaction rate theory which predicts the ratio of rates to be equal to the ratio of the reduced masses.

Foldiak and Horvath[41] studied the radiolysis of cyclopropane–propane and cyclopropane–propene mixtures. Horvath and coworkers[42] reported on the comparison between photolysis and radiolysis of the mixture cyclopropane–propane system.

Figure 2 shows Foldiak and Horvath's[41] results for radiolysis of a cyclopropane–propane mixture at 30–35°C. The mixture contained both liquid and gaseous hydrocarbons with a volume ratio of the two phases of about 1:1. The figure shows that cyclopropane gives most of the ethylene and acetylene, whereas hydrogen and methane are produced mainly from propane. C_4 and C_5 products are produced only in pure propane but not from pure cyclopropane. The shape of the curves describing the yields of all products as well as the deviation from linearity can be explained by the differences between the ionization potentials (propane—11.08 eV, cyclopropane—10.09 eV)[43], together with the reactions of the decomposition of excited propane and cyclopropane molecules. In order to interpret the maximum observed in the yields of ethylene, acetylene, and butanes, some sort of interaction between the two parent components or between the intermediates produced from them should be assumed, besides energy and charge transfer. One possibility for this interaction is given in equations 39–43:

$$C_3H_8^+ + c\text{-}C_3H_6 \longrightarrow C_3H_8 + c\text{-}C_3H_6^+ \tag{39}$$

$$c\text{-}C_3H_6^+ + C_3H_7^\cdot \longrightarrow c\text{-}C_3H_6 + C_3H_7^{+\cdot} \tag{40}$$

$$C_3H_7^\cdot + CH_3^\cdot \longrightarrow C_4H_{10} \tag{41}$$

$$C_3H_7^{+\cdot} + e^- \longrightarrow C_2H_4^* + CH_3^\cdot \tag{42}$$

$$C_2H_4^* \begin{cases} \xrightarrow{\text{stabilization}} C_2H_4 \\ \longrightarrow 2H^\cdot\ (\text{or } H_2) + C_2H_2 \end{cases} \tag{43}$$

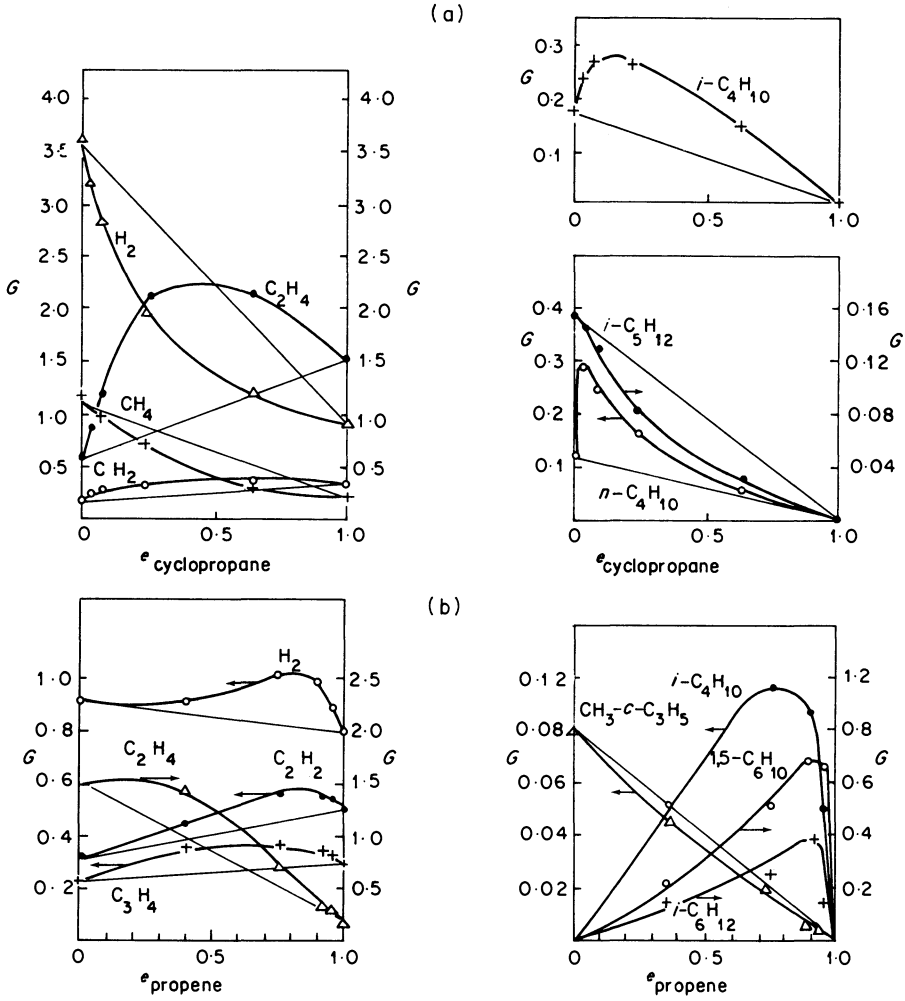


FIGURE 2. *G*-values of the various products in the radiolysis of (a) propane–cyclopropane mixtures, (b) propene-cyclopropane mixtures as a function of the concentration (e = mole fraction). (Taken from Foldiak and Horvath[41] with the permission of the authors)

Another possible interaction is given in equations 44–46:

$$C_3H_8^* + c\text{-}C_3H_6 \longrightarrow C_3H_8 + c\text{-}C_3H_6^* \tag{44}$$

$$c\text{-}C_3H_6^* \longrightarrow C_2H_4^* + \ddot{C}H_2 \tag{45}$$

$$:CH_2 \xrightarrow[H]{\text{abstraction of}} \dot{C}H_3 \xrightarrow[H]{\text{abstraction of}} CH_4 \tag{46}$$

The maxima of both ethylene and acetylene yields lie at an identical cyclopropane concentration, supporting Foldiak and Horvath's suggestion that they are formed from

the same intermediates. The addition of cyclopropane to propane to bring the maximum production of C_2H_4 and C_2H_2 increases their yields by 1.2 and 0.2 G units respectively, indicating that the excited biradical intermediate $C_2H_4^*$ decays 6/7 to C_2H_4 and 1/7 to C_2H_2.

The similar shapes of the plots of the yields of n-butane and isobutane as well as the maxima being at nearly identical cyclopropane concentrations indicate that the excess yield of both hydrocarbons is formed in the same reaction. This may be, for example, an insertion of a carbene into a C–H bond in propane, either in the CH_3 group or in the CH_2 group (equation 47):

$$CH_3CH_2CH_3 + :CH_2 \longrightarrow \begin{cases} \rightarrow CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_3 \\ \rightarrow CH_3CH_2CH_2CH_3 \end{cases} \qquad (47)$$

Both products are formed in excited states and can also be isomerized before stabilization by collision. When cyclopropane concentration increases the carbene favors other reactions thus leading to lower yields of butanes.

Figure 2 also gives the G-values of the various products in the radiolysis of mixtures of cyclopropane–propene. The maximum in the acetylene yield is at a cyclopropane molar fraction of 0.75 and in the ethylene yield at cyclopropane molar fraction of 0.25 indicating probably that they are produced in competing reactions of the same intermediate. The curve of the yields of isobutane, 4-methyl-1-pentene and 1,5-hexadiene indicate bimolecular reactions since none of them is formed in the pure components. Foldiak and Horvath[41] suggested that the formation of these hydrocarbons may be explained by combination reactions between the reactive intermediates existing in high steady state concentrations in the system, as in equations 48 and 49:

$$2CH_2=\dot{C}HCH_2 \rightarrow CH_2=CHCH_2CH_2CH=CH_2 \qquad (48)$$

$$CH_2=CHCH_2 + CH_3\dot{C}HCH_3 \rightarrow CH_2=CHCH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_3 \qquad (49)$$

However, there is no explanation why these reactions, especially reaction 48, will not occur in the pure components.

Scala and coworkers[44] studied the liquid phase radiolysis at 77 K of 3-methylpentane or 2-methylbutane with cyclopropane $-d_6$(0.3–21 mol%); the only deuterated propane formed was $CD_2HCD_2CD_2H$. The fact that no other deuterium-labeled propanes were formed indicates that the process cyclopropane → propane occurred in an one-step mechanism in which H_2 is transferred to c-C_3D_6. Photochemical experiments proved that this H_2 transfer is due to an ion; photolysis of i-$C_5H_{12} + c$-C_3D_6 at 77 K led to $CD_2HCD_2CD_2H$ only when using an argon lamp (11.5–11.7 eV) but not with a lower energy xenon lamp (8.4 eV) which cannot induce ionization. Another proof for the ionic nature of the reaction is the observation that addition of CCl_4 increases considerably the yield of $CD_2HCD_2CD_2H$ (the G-value for 3 mol% of c-C_3D_6 mixture increased from 0.7 to 2.1–2.9 depending on CCl_4 concentration). CCl_4 is an efficient electron scavenger[45] and its addition decreases the probability that the parent ion will be neutralized by the electrons prior to their reaction with c-C_3D_6. An additional proof for the formation of $CD_2HCD_2CD_2H$ by an ionic precursor is found in the radiolysis of the mixture $C_5H_{12} + c$-$C_3D_6 + CCl_4$; addition of methanol to this mixture reduces the yield of $CD_2HCD_2CD_2H$. Due to its high proton affinity methanol abstracts proton from the parent ion[46], thus reducing the concentration of the ions which can transfer H_2 to cyclopropane. The yield of $CD_2HCD_2CD_2H$ is linearly dependent on the square root of

the concentration of c-C_3D_6[44], a dependence which is predicted for scavenger competition with the geminate recombination.

Rzad and Schuler[47] studied the radiation chemistry of a solution of ^{14}C-cyclopropane in hexane over the concentration range 10^{-4} to 10^{-1} M. The main radioactive products, which appear to result from ion molecule reactions, are propane formed by H_2 transfer (50%)and by H transfer (20%) and mixed nonanes (30%) formed by the addition of C_3H_6 unit to a hexyl ion. At the lower concentrations, very pronounced dose dependence of the yields was observed. This was ascribed to a competitive formation of olefins in the radiolysis. For cyclopropane–cyclohexane solutions the chemical processes seem to be considerably more complicated. The observed yield of total radioactive products extrapolated to zero concentration of cyclopropane are 0.05 and 0.11 G units for hexane and cyclohexane, respectively. These limiting yields are of the order of magnitude of and appear to be related to, the free ion yields in these systems. Since cyclopropane was found to react with hydrocarbon ions[48,49] it is used quite often as a scavenger for positive ions, as in the work of Davids and coworkers[50].

II. HOT ATOM CHEMISTRY OF CYCLOPROPANE

A. Introduction

When an atom has undergone a nuclear transformation (either nuclear reaction or radioactive decay), it usually acquires high kinetic energy from the recoil process, or high electric charge, or both. A very high kinetic energy ($> 10^4$ eV) is obtained in a nuclear reaction in which a heavy particle (not an electron) is emitted as for example tritium atoms produced by the ^{3}He(n, p) T reaction. Lower energy, but still few hundreds of eV, is obtained in the radiative capture (n, γ) reaction. Lower energies, few eV or few tens of eV, are obtained in the case of electron capture, isomeric transition, and β-decay. The main characteristics of β-decay for chemical purposes are (1) the change in nuclear charge, followed by 'shaking' of the electron shell by this abrupt change in the nuclear charge, (2) electronic, vibrational and rotational excitation and (3) acquiring of momentum of the recoil process to compensate for the momentum of the escaping nuclear electron. Electron capture and isomeric transition are accompanied by multiple charging following vacancy production, internal conversion and the Auger consequences plus some effects of recoil momentum. Thus, the characteristic chemical behavior is that of charged atoms with kinetic energy higher than thermal. Atoms formed with an energy well in excess of the ambient thermal energy are called hot atoms. Such atoms dissipate most of their kinetic energy in the medium, producing radiolytic changes in the surrounding system, very similar to those found in radiation chemistry, and eventually become stabilized through chemical reactions. If the hot atom produced is not radioactive, its chemistry cannot be studied as the amounts of its products are very low, and are obscured by the products of the radiolytic process. When the hot atom produced is radioactive, we can follow its fate until it becomes chemically combined. The occurrence of reactions of the highly kinetic energy atoms before reaching thermalization can be proved mainly by one or more of the following three ways:

(1) Formation of products different from those formed in thermal processes.

(2) The effect of noble gas moderators. In a gaseous thermal reaction the addition of noble gas to the system should not change the yield of the various products, unless causing stabilization of excited products. However, in the case of hot atoms, the presence of noble gas leads to collisions of the hot atom with the noble gas molecules and consequently to a loss of its kinetic energy. Thus, the addition of noble gas moderators decreases the yields of the products formed by the hot atoms while still having high kinetic energy.

(3) The effect of scavengers. The presence of a compound with a high rate constant for reaction with thermal atoms (scavengers) in minute concentration will decrease substantially the yields of thermal chemical reactions and only very little the yields of the hot reactions. In the case of product produced both by thermal and hot reactions, the addition of minute concentration of scavengers (1–2 % mole fraction) is necessary for elimination of the thermal reaction and to enable to measure only the yield of the hot reaction.

B. Gas Phase

1. The reaction of hot tritium atoms with cyclopropane

Hot tritium atoms are formed in the gaseous phase with very high kinetic energy ($> 10^5$ eV) through reactor neutron irradiation of ^{3}He: ^{3}He(n, p) T. Hot tritium atoms react with saturated hydrocarbons in one of the following three reactions: hydrogen abstraction (equation 50), hydrogen substitution (equation 51) and alkyl substitution (equation 52)[51, 52]. The asterisks designate an energetic species:

$$T^* + RH \longrightarrow HT + R \tag{50}$$

$$T^* + RH \longrightarrow RT + H \tag{51}$$

$$T^* + R^1\text{–}R^2 \longrightarrow R^1T + R^2 \tag{52}$$

In the case of cyclopropane reaction 51 will lead to T-cyclopropane (c-C_3H_5T) while reaction 52 will lead to ring-opening and the formation of the radical $CH_2TCH_2\dot{C}H_2$. This radical is highly excited and can be decomposed by breaking either a C–C or a C–H bond (equations 53 and 54):

$$CH_2TCH_2\dot{C}H_2 \longrightarrow \dot{C}H_2T + CH_2{=}CH_2 \tag{53}$$

$$CH_2TCH_2\dot{C}H_2 \longrightarrow CH_2T\text{–}CH{=}CH_2 + H \tag{54}$$

However, the product $CH_2TCH{=}CH_2$ must not be due only to reaction 54 as it can be produced also by the isomerization of the product of reaction 51 if it is in an excited state (equation 55):

$$\longrightarrow CH_2TCH{=}CH_2 \tag{55}$$

This reaction was studied thermally[53] and found to have relatively low activation energy. In the case of thermal deuterium atoms, they did not show any exchange of D for H in the cyclopropane molecules[54], indicating that reaction 51 has high activation energy. The kinetic energy of the hot tritium atom was found[55, 56] to overcome this activation energy, as 16 % of the hot tritium produced in the presence of c-C_3H_6 is incorporated in T-cyclopropane (equation 56):

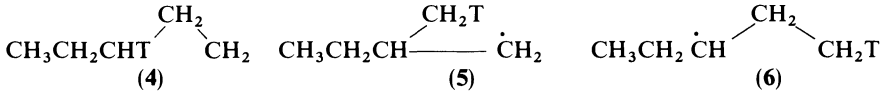
$$T^* + c\text{-}C_3H_6 \longrightarrow c\text{-}C_3H_5T + H \tag{56}$$

Similar yields of c-C_3H_5T were found in the presence and in the absence of the efficient radical scavengers oxygen or nitric oxide, indicating that the formation of c-C_3H_5T does not involve the reaction of thermal free radicals. The addition of noble gas, ^{4}He, to the system decreased the yield of c-C_3H_5T, proving that its formation is due to a hot reaction influenced by a moderator gas. Other tritium-labeled hydrocarbons, mainly methane, ethane, propane, butane and isopentane, are also formed but in yields smaller than T-cyclopropane (10–40 % of that of c-C_3H_5T). However, the addition of nitric oxide decreases their yields almost to zero indicating that they are formed not by hot atoms but rather by reactions of thermal radicals. The yield of c-C_3H_5T was found to increase with

gas pressure indicating that the c-C_3H_5T is formed in an excited state and that there is a competition between collisional de-excitation and decomposition, probably through isomerization to T-propylene. This isomerization can explain the formation of T-propylene (its yield is about 10–20% of T-cyclopropane) and there is no proof for its formation through reaction 52—which is a ring-opening. The highest yield of T-labeling is of HT due to reaction 50; 30–60% of the total T atoms appear as HT. A study of the yield of HT for various hydrocarbons, including cyclopropane, in systems including radical and ion scavenger and high pressure of moderator showed that the yield of HT per C–H bond is a monotonous decreasing function of the C–H bond dissociation energy[57–59].

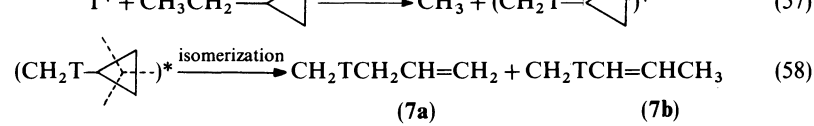
2. *The reaction of hot tritium atoms with substituted cyclopropanes*

In the case of cyclopropane there was no clear proof for reaction 52 with ring-opening. The same product $CH_2TCH{=}CH_2$ can be formed also by isomerization of c-C_3H_5T, and the conclusion was that there is not, or very little, ring-opening of cyclopropane by reaction with hot T atom. Tang and Rowland[60] studied the reaction of T atoms with alkyl-substituted cyclopropanes in order to clarify the problem of ring-opening. They used ethylcyclopropane (EC), *cis*-1,2-dimethylcyclopropane (*cis*-DMC) and *trans*-1,2 dimethyl-cyclopropane (*trans*-DMC). In all these cases, the major product is the labeled parent molecule but labeled C_4 and C_5 olefins are also produced with yields of several percents. In the case of EC, the addition of T atom together with ring-opening can produce excited radicals (**4**–**6**).

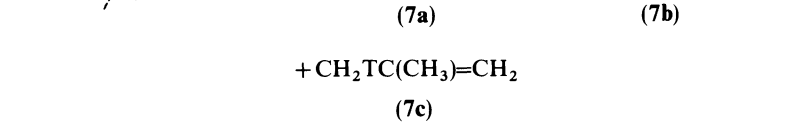


(4) **(5)** **(6)**

These excited radicals can be stabilized by intramolecular cleavage of either a C–H or a C–C bond. The radicals which are stabilized by de-excitation collision are removed from the system by the radical scavenger. Breaking C–H bonds will produce T-labeled pentenes which cannot be distinguished from those formed by isomerization of excited T-substituted ethylcyclopropane, the major product. Thus the pentenes cannot be utilised to prove the extent of ring-opening. Breaking the weaker C–C bonds will form $CH_3CH_2CHT^{\cdot} + C_2H_4$ from (**4**), $C_2H_5^{\cdot} + CH_2TCH{=}CH_2$ from (**5**) and $CH_3^{\cdot} + CH_2{=}CHCH_2CH_2T$ from (**6**). Those T-substituted propene and butene cannot be produced from isomerization of excited T-substituted EC and hence can be used to measure the extent of direct ring-opening. However, T-substituted butenes and propene can be formed also by energetic substitution of tritium for alkyl group (cf. equation 52) in the side chain, as in eqautions 57 and 58:



$$T^* + CH_3CH_2\text{—}\triangleleft \longrightarrow CH_3^{\cdot} + (CH_2T\text{—}\triangleleft)^* \qquad (57)$$



$$(CH_2T\text{—}\triangleleft)^* \xrightarrow{\text{isomerization}} CH_2TCH_2CH{=}CH_2 + CH_2TCH{=}CHCH_3 \qquad (58)$$

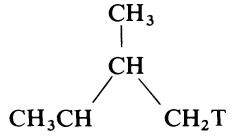
(7a) **(7b)**

$$+ CH_2TC(CH_3){=}CH_2$$

(7c)

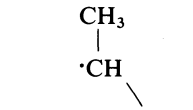
Reactions 57 and 58 will form T-labeled 1-butene, 2-butene and isobutene, as was found for thermal isomerization of methylcyclopropane[53] whereas the direct ring-opening will form only T-substituted 1-butene. The experimental observation that T-substituted 1-butene was formed with a yield one order of magnitude higher than that of 2-butene and

isobutene together indicates that the main source for T-substituted butene is by direct ring-opening followed by stabilization of the excited radical through methyl radical splitting. Similarly, in the case of 1,2-dimethylcyclopropane, T addition with ring-opening will lead to the radicals **8a**–**8c** and to products derived from equations 59–61:



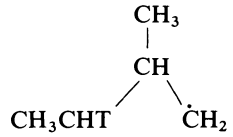
(8a)

$$\longrightarrow \quad \begin{matrix} CH_2T + CH_3CH{=}CHCH_3 \\ \text{or} \\ CH_3^{\cdot} + CH_3CH{=}CHCH_2T \end{matrix} \qquad (59)$$



(8b)

$$\longrightarrow \quad CH_3\dot{C}HT + CH_3CH{=}CH_2 \qquad (60)$$



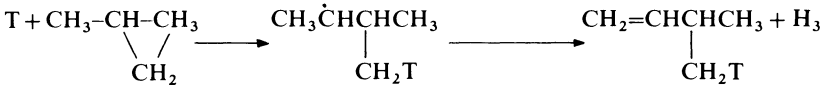
(8c)

$$\longrightarrow \quad CH_3^{\cdot} + CH_3CHTCH{=}CH_2 \qquad (61)$$

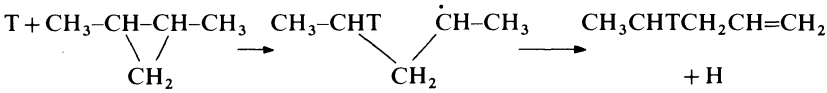
Thus, ring-opening is not expected to lead to isobutene while alkyl substitution, followed by isomerization, will lead also to isobutene. For *cis*-DMC only T-substituted 1- and 2-butenes were found experimentally. For *trans*-DMC T-substituted isobutene was also observed; however, its yield is one order of magnitude less than the yields of 1-butene or 2-butene. It should be noted that the observation of thermal isomerization of methylcyclopropane[53] also indicates that the yield of isobutene will be 10–20% of that of 1-butene or 2-butene, a fact which Tang and Rowland did not know, at that time[60], although it had been published in 1964[61], and thus the results on *trans*-DMC do not prove direct ring-opening. The other evidence serves as conclusive proof for direct ring-opening; however, its yield is less than 10% of the direct T for H substitution which leads to the T-substituted parent molecule.

The yield of T-substituted C_5 olefins produced both by isomerization of the parent molecule and by ring-opening followed by C–H bond rupture is also less than 10% of the yield of the T-substituted parent molecule. In the case of ethylcyclopropane, it cannot be distinguished whether the T-substituted C_5 olefins were produced by isomerization of the parent molecule or by ring-opening followed by C–H bond rupture, since both processes will lead to the same four isomers of T-pentene. On the other hand, structural isomerization of dimethylcyclopropane (either *cis* or *trans*) will lead to only four isomers of T-substituted pentenes (2-methyl-1-butene, 2-methyl-2-butene and *cis* + *trans*-2-pentene)[62], whereas ring-opening followed by C–H bond rupture will lead to, besides these four isomers together, two other isomers (1-pentene and 3-methyl-1-butene) (equations 62

and 63):



(62)



(63)

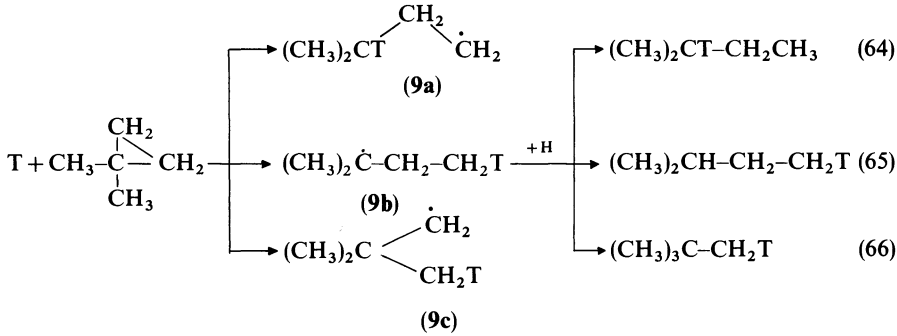
Both T-substituted 1-pentene and 3-methyl-1-butene were observed in yields comparable to the other T-pentene isomers. This observation clearly indicates that the primary source of T-pentene in these systems is through the loss of H atoms from the excited radicals formed by hot tritium addition with opening of the cyclopropane ring. The almost lack of isomerization of the T-substituted parent molecule set an upper limit for the energy left in the T-substituted parent molecule due to the reaction with energetic tritium; the upper limit is equal to the activation energy for isomerization (65 kcal mol^{-1} for cyclopropane and methylcyclopropane and about 62 kcal mol^{-1} for ethylcyclopropane and dimethylcyclopropane[53].

The reaction of T with the geometrical isomers of DMC lead mainly to the T-substituted isomer with configuration similar to the reactant; however, there is a 5% *trans* contamination in the case of T + *cis*-DMC and an 8% *cis* contamination in the case of T + *trans*-DMC. In other hot T for H substitution, it was found[63,64] that there is retention of the configuration. Here, however, substitution with inversion or late isomerization of the T-substituted parent molecule cannot be distinguished. The activation energy for the thermal isomerization of *cis* → *trans* and *trans* → *cis* is about 2 kcal mol^{-1} lower than that of isomerization of pentenes.

Besides the T-cyclopropanes, T-butenes and T-pentenes, several highly unsaturated tritium-labeled products, including acetylene, allene, propyne and 1,3-butadiene were observed in the hot T reaction with EC and DMC. Except for T-acetylene, whose yield is about 10% of the substituted parent molecule, the yields of the other products are very low.

Su and Tang[65] studied the reaction of hot T atoms with 1,1-dimethylcyclopropane in order to ascertain where the ring is most probably opened. While Tang and Rowland did not differentiate between T-butenes or T-pentenes, having tritium atoms on different portions of the molecule[60], Su and Tang did it by using proton exchange with H_2SO_4[65]. In isobutane and isopentane all the hydrogen (T) atoms, except the tertiary ones, would be exchanged with those of sulfuric acids[66–68]. By measuring the specific activity of T-isopentane before and after proton exchange, the yields of both primary and tertiary tritium atoms are obtained. The yields of tritiated products both in non-scavenged systems as well as in systems scavenged either by O_2 or H_2S were measured. O_2 scavenges the radicals and removes them from the determination system (gas chromatograph); but it does not influence the yields of the direct products and those obtained by isomerization through biradical mechanism. Radicals which result from ring-opening are removed by O_2 only if they are thermalized. In cases where they are excited, they will be stabilized by C–H or C–C bond rupture as was found in previous studies. In the H_2S-scavenged system the radicals will abstract hydrogen atoms from H_2S (which has easily abstractable hydrogen atoms)[69,70]. Thus the radicals formed by ring-opening will result in T-pentanes. In the presence of O_2 as a scavenger, the yield of T-pentenes is about 15% of the T-substituted parent molecule, but most of it comes from ring-opening and not from isomerization of methylcyclopropane, which is not expected to give so high a percentage of isobutene. Including all products, which might possibly come from unimolecular isomerization and

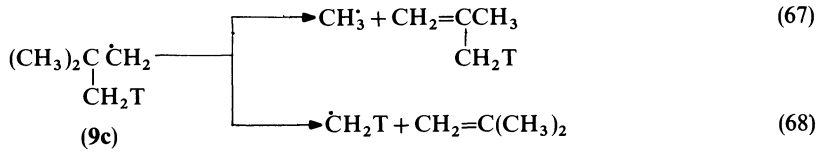
decomposition, an upper limit for the yield of non-stabilized T-substituted parent molecules of 30% is observed. The main products, whose yields increased upon the addition of H_2S, are HT and CH_3T and T-isopentane, which come from CH_2T and *i*-$C_5H_{10}T$ radicals. The cyclopropyl ring in 1,1-dimethylcyclopropane (DMC) can be opened by the three modes shown in equations 64–66:



Unless the position of the T atom can be determined, reactions 64 and 65 give the same product. The yield of reaction 66 is about 1% of that of the sum of 64 and 65. This is probably mainly due to the short half-life of the neopentyl radical which, due to lower C–C bond strength, can be easily decomposed to $CH_2T + CH_2{=}C(CH_3)_2$.

The other important product, CH_3T, coming from the CH_2T radical, is formed by C–C bond rupture of either **9b** or **9c**.

Another observation was that the yield of T-substituted parent molecule (percent of T atoms incorporated in 1,1-dimethylcyclopropane) was the highest in the case of H_2S-scavenged system. Assigning the H_2S-scavenged yield as unity leads to a yield of 0.89 and 0.77 for the non-scavenged and O_2-scavenged systems, respectively. The observation of higher yield of the parent molecule in the H_2S-scavenged system was ascribed to C–H bond rupture in the hot parent molecule, so as to yield tritiated radicals which, in the case of H_2S, abstract an hydrogen atom from H_2S giving back the parent molecules. In the other systems these radicals, or at least a part of them, do not give back the parent molecule, but rather form different compounds. This explanation of Su and Tang[65] suffers from the drawback that the rupture of a C–H bond required a much higher energy than the structural isomerization, thus assuming 27% of C–H bond rupture, when compared to only 10–15% of structural isomerization seems unreasonable. An alternative explanation might be that the direct displacement of two hydrogen atoms by the hot tritium atom leads directly to the tritiated radical of the parent molecule. This displacement reaction of two atoms, in the attack of hot atoms, is known both for hot tritium and hot halogen atoms[51]. In order to normalize the yields of other products in the three systems, all the yields are multiplied by the ratio of the yields of the T-substituted parent molecule. Since CH_3T is also formed in the O_2-scavenged system, its yield must be substracted from that in the H_2S-scavenged system in order to receive the yield of CH_2T radicals. Radical **9c** in reaction 66 may decompose by two different routes (equations 67 and 68):



By neglecting any tritium isotope effect, the yield of reaction 67 should be twice of that of 68 due to the presence of two CH_3 groups, compared to only one CH_2T group. Consequently, the yield of $\dot{C}H_2T$ from reaction 68 is one-half of the yield of T-isobutene formed through ring-opening. The substraction of this yield of $\dot{C}H_2T$ from the total yield of $\dot{C}H_2T$ gives the yield of $\dot{C}H_2T$ from radical **9b**. The T-isopentane from reactions 64 and 65 have tritium atoms on different positions of the species, tertiary in 64, which cannot be exchanged with the protons of sulfuric acid (through a carbonium ion intermediate), and primary exchangeable in 66. The measurement of the specific activity of T-isobutane before and after H_2SO_4 treatment show that only 9.6% of the T-isobutane comes from reaction 64. By combining the yields of all the products produced from the radicals formed by reactions 64, 65 and 66 it can be seen that their yields are in the ratio of 20:179:28. This indicates that the hot tritium atom will attach itself to a carbon atom which either possesses a higher electron density, or is less sterically hindered, or even both. The breaking of the bond with the tertiary carbon atom is due to its lower bond strength.

3. The reaction of hot tritium atoms with cyclopropyl bromide

Davanloo and Wai[71] studied the reaction of hot tritium from the $^3He(n, p)T$ reaction with gaseous cyclopropyl bromide. Table 6 gives the ratio of the yields in the presence of I_2 as a scavenger. Due to the low vapor pressure of c-C_3H_5Br at room temperature, the effect of stabilization was observed by the addition of CH_3Br. It acts both as a stabilizer and as a moderator, thus reducing the yields of all hot products, and the important results are the ratios of the yields of the various organic products.

TABLE 6. Ratio of the yields of the various tritiated organic products in the reaction of hot T with c-C_3H_5Br (normalized to yield of c-C_3H_4TBr = 1.0)[a]

System / Product	13.3 kPa c-C_3H_5Br	13.3 kPa c-C_3H_5Br + 50.5 kPa CH_3Br	4.12 kPa c-C_3H_5Br + 15.3 kPa CH_3Br
CH_2TBr	0.22	—	—
T-Vinyl bromide	0.16	—	—
T-1-Bromopropene	0.22	0.079	0.13
T-2-Bromopropene	0.10	0.026	0.062
T-Allyl bromide	0.79	0.55	0.78
T-Ethylene	0.25	—	—
T-Propene	0.64	0.50	0.69
c-C_3H_5T	1.11	1.16	1.19

[a] ^3He pressure = 2.4 kPa, I_2 at its vapor pressure.

These results clearly indicate that the formation of the T-bromopropenes and T-allyl bromide is due to isomerization of the excited c-C_3H_4TBr, as their formation is retarded by increasing the pressure. While the yield of tritiated olefins formed by the reaction of hot tritium with cyclopropane or alkyl-substituted cyclopropane is less than 10–20% of the tritiated parent molecule it can be seen that in the case of T-cyclopropyl bromide, it is more than 100% (the sum of allyl bromide and bromopropenes). This can be due to the lower activation energy for isomerization of cyclopropyl bromide, 47 kcal mol^{-1} [72], when compared to that of cyclopropane, 65 kcal mol^{-1}. The ratio of T-propene to c-C_3H_5T is about 0.6. Davanloo and Wai assumed that all T-propene was formed through the isomerization of c-C_3H_5T and calculated, from the dependence of the ratio of the yields of T-propene and c-C_3H_5T on total pressure, that the median excitation energy in the c-C_3H_5T is 88 ± 6 kcal mol^{-1} (3.8 ± 0.3 eV)[71]. However, they neglected the possibility that

T-propene was formed by the T addition and the ring-opening. Due to the fact that the C–Br bond is weaker than the C–H bond, the T addition and ring-opening will lead mainly to T-propene and not to T-bromopropenes. This might also be the explanation why the ratio, T-propene to c-C_3H_5T, is much higher (0.6) in the reaction of hot T with cyclopropyl bromide, in comparison with the reaction of T with cyclopropane (0.14). Another possible explanation is that T for Br substitution leaves more energy in the molecule than T for H substitution.

Assuming that the reactivities of the five C–H bonds in cyclopropyl bromide are equivalent and considering also the isomerization products, the relative yield of T for Br versus T for H exchange in cyclopropyl bromide is 4.2. This might be due to the weaker C–Br bond as was suggested by Tang[73].

The ratio of T-1 bromopropenes (*cis* and *trans*) to T-allyl bromide is lower than the ratio of their thermodynamic equilibria[74,75], indicating that equilibrium is not reached in isomerization and that T-allyl bromide is formed preferentially due to faster migration of the Br atom resulting from the weaker C–Br bond.

4. Hot atom reactions from β-decay of tritium

Usually, when referring to hot atoms produced by β-decay, it means the sequence of equation 69:

$$A \xrightarrow{\beta} B \xrightarrow{\beta} \tag{69}$$

B is formed by β-decay of A and, due to the recoil, it gets a high kinetic energy. B itself should be radioactive, since otherwise it is not possible to determine analytically the yields of the products of B. The situation is different in the case of decay of tritium nuclide. The decay (equation 70):

$$T \rightarrow {}^3He + e^- \tag{70}$$

produces helium atoms which do not react with the surrounding molecules and in any case they are not radioactive, preventing their determination. However, when using a T_2 molecule, the decay of one tritium atom might lead to a higher than thermal kinetic energy of another tritium atom, due to bond rupture. Two different mechanisms of labeling are prevalent in the decay of tritium gas in an organic media: (1) radiolytic labeling, due to radiolysis by e^- (equation 71) and (2) hot labeling due to hot tritium atoms.

$$e^- + T_2 \rightarrow \text{excited states or radicals} \tag{71}$$

The yields, due to the first process, depend on T_2 concentration, whereas the second process is independent of the T_2 concentration. Radiolytic labeling is inhibited by radical scavengers, whereas hot labeling occurs also in the presence of scavengers.

Gant and Yang[87] studied the decay of gaseous T_2 in cyclopropane (cyclopropane pressure more than 100 times that of T_2). The main products are tritiated cyclopropane, propane, propene, ethylene, ethane and acetylene. Table 7 gives the yields of the main products as fractions from the number of tritium atoms, incorporated into these compounds.

The yields of propane and propene were found to be linearly dependent on the concentration of tritium. Temperature has no effect on the initial rate of formation of propane or propene. NO inhibits completely the formation of propane, but only partly that of propene. Propane can still be formed by hot labeling, through ring-opening and subsequent abstraction of hydrogen—a process which is inhibited by a radical scavenger. Isobutane formation was independent of tritium concentration and temperature and was completely inhibited by the addition of nitric oxide. In the presence of NO, the yield of

TABLE 7. The yields of the main products in the system T_2 + cyclopropane[a]

Experimental conditions			Yields			
Tritium activity (Ci)	Temperature (°C)	Scavenger	c-C_3H_6	C_3H_8	Propene	Ethylene
4	0	—	0.104	0.245	0.180	0.046
4	Ambient	—	0.135	0.237	0.178	0.051
4	Ambient	NO	0.056	0	0.034	0.30
8	Ambient	NO	0.056	0	0.053	0.053

[a] The pressure of cyclopropane is 93 kPa, and NO pressure when present as scavenger is 56 kPa.

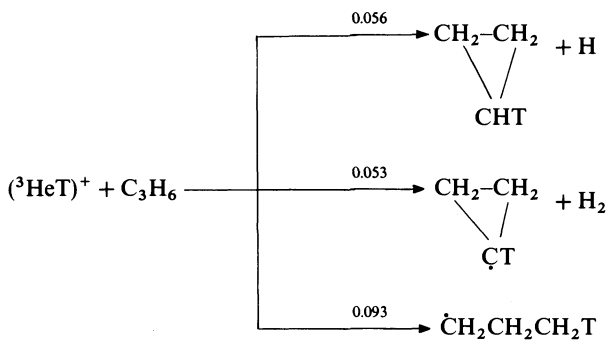
ethylene is independent of the reaction time; however, in the absence of nitric oxide, the yield sharply decreases with the reaction time, due to the secondary reaction of C_2H_4 with radicals in the system. In both cases, the yield increases linearly with tritium concentration. The yield of ethane increases with the reaction time, indicating thereby that ethane is formed by a secondary process involving a radiolysis product (most likely ethylene).

The yields of labeling by the two mechanisms is given in Table 8.

TABLE 8. Yields of labeling by the two mechanisms

	Product			
	Cyclopropane	Propane	Propene	Ethylene
Mechanism 1	—	0.046	0.038	0.076
Mechanism 2	0.109	0.052	0.041	0.022

The reactions involved in hot labeling are given in equation 72.



(72)

The numbers above the arrows are the yields of the various processes. Thus, the extent of ring-opening is much higher than in $^3He(n, p)T$ production of hot T atom, probably due to the neutral character of the T atom in the latter case, whereas in the former it is positively charged.

The radical $CH_2TCH_2\dot{C}H_2$ is not removed completely by NO since NO not only combines with it but can also abstract hydrogen and produce a tritiated propene

(equation 73):

$$NO + CH_2TCH_2CH_2^{\cdot} \rightarrow HNO + CH_2{=}CHCH_2T \quad (73)$$

5. *The reaction of hot bromine atom with cyclopropane and cyclopropyl bromide*

Wai and Jennings[76] studied the yields of the products of ^{80m}Br produced by the nuclear reaction $^{79}Br(n,\gamma)^{80m}Br$ with gaseous cyclopropane. Saeki and Tachikawa[77] used ^{80}Br produced mainly from $^{79}Br(n,\gamma)$ ^{80}Br and very little from $^{80m}Br(I.T.)^{80}Br$. De Jong and coworkers used $^{76,77}Br$ from the decay by electron capture and β^+ of $^{76,77}Kr$[78]. The (n,γ) reaction left the hot bromine atom with an energy of more than a hundred eV due to recoil in order to compensate for the momentum of the emitted photon. The chemical consequences of isomeric transition is due to inner shell ionization[79]. The highly converted isomeric transition of ^{80m}Br gives rise to Auger process and vacancy cascades, leading to multiply charged daughter ions. Charge distribution and Coulomb repulsion cause the molecule containing the ^{80}Br to explode, thus creating charged fragment ions. Charge spectrometric measurements showed that ^{80}Br ions, with a predominant charge of +7 are formed[80]. The ^{80}Br ions also possess kinetic energies of several eVs, resulting from Coulomb repulsion. Not unlike internal conversion, electron capture decay gives rise to inner shell vacancy, followed by Auger charging, thus leading to multiply charged ions and excess kinetic energy due to Coulomb repulsion.

The most important result of Wai and Jennings[76] is that no detectable amount (< 0.1 %) of labeled cyclopropyl bromide (c-$C_3H_5^{80m}Br$) was found. Instead, the isomerization product ^{80m}Br–allyl bromide was found as the major product (14 %). This result suggests that nearly every excited c-$C_3H_5^{80m}Br$ molecule formed by recoil ^{80m}Br substitution for H in the cyclopropane, undergoes secondary structural isomerization. This is in contrast to the very low yield of structural isomerization in the case of T for H substitution in cyclopropane and the isomerization of half of the molecules in the T for H substitution in cyclopropyl bromide. This might be due to higher energy left in the product in the case of reaction with the heavier Br projectile, or due to the different physical nature of the two reacting species involved, ^{80m}Br reacting as a positive ion while T is reacting as an atom. Wai and Jennings gave only the yield of ^{80m}Br–allyl bromide and did not mention at all ^{80m}Br–1-bromopropene or -2-bromopropene[76]. It is not clear if they are not formed (which will raise the question why they are formed in T for H substitution in cyclopropyl bromide) or if they were measured together with ^{80m}Br–allyl bromide. The yields of the main organic products in the case of ^{80m}Br + cyclopropane are: allyl bromide, 1.42 %; methyl bromide, 0.25 %; vinyl bromide, 0.1 %. While these authors did not find any stabilization of excited cyclopropyl bromide (at a pressure of 95 kPa) Saeki and Tachikawa studied pressure effects more thoroughly and observed that at 120 kPa 10.2 % of the total organic yield consisted of cyclopropyl bromide (at 95 kPa 8.8 % of the total organic yield was the parent compound)[77]. There is no reason for this difference. De Jong[78] wrote that the difference between the two experiments is that Saeki and Tachikawa used CH_3Br and Wai and Jennings used Br_2 as the bromine source.

However, Saeki and Tachikawa studied both Br_2 and CH_3Br as bromine sources at a pressure of 13 kPa and found the same yield of 6–7 % of the total organic yield for c-$C_3H_5^{80}Br$. They also did not mention ^{80}Br–1-bromopropene and -2-bromopropene[77] so it is not clear if these are not formed or cannot be resolved from the ^{80}Br–allyl bromide. Saeki and Tachikawa used I_2 in pressure of the vapor pressure at room temperature as scavenger and 1 kPa of CH_3Br as bromine source. The pressure of the cyclopropane was from 13.3 to 120 kPa. The main hot product found was $CH_2^{80}Br^{\cdot}$ (appearing as $CH_2^{80}BrI$) and its yield decreased with the increasing pressure of c-C_3H_6. This decrease in the yield of $\dot{C}H_2^{80}Br$ (from 12.5 % to 8.2 %, when the pressure is changed from 13.3 to 120 kPa) is compensated by a parallel increase in the yield of ^{80}Br–allyl bromide (from 0.83 % to

5.32 %). The yield of $c\text{-}C_3H_5^{80}Br$ increases with pressure from 13.3 to 100 kPa but decreases at higher pressure although all the yields at pressures above 50 kPa are the same within their experimental error. The yields of $CH_3^{80}Br$ and $CH_2{=}CH^{80}Br$ are independent of the pressure.

The possibility of decomposition of the excited $c\text{-}C_3H_5^{80}Br$ to give bromocarbene (equation 74)

$$(c\text{-}C_3H_5^{80}Br)^* \rightarrow CH_2{=}CH_2 + {:}CH^{80}Br \tag{74}$$

was studied by addition of isobutene which has a high reactivity towards bromocarbene. 1-Bromo-2,2-dimethylcyclopropane was formed with a yield of only 0.9 % indicating that this is not the main decomposition pathway of the primary substituted product. The yield of $CH_2{-}CH^{80}Br$ is about 0.3 %, and thus the decomposition via equation 75

$$(c\text{-}C_3H_5^{80}Br)^* \rightarrow CH_2{=}CH^{80}Br + {:}CH_2 \tag{75}$$

is also of minor importance, and thus it can be expected that the excited parent molecule will be isomerized to ^{80}Br–allyl bromide. However, this will mean that the yield of ^{80}Br–allyl bromide should decrease with increasing pressure while it was found to increase with increasing pressure. The only product whose yield decreases with pressure is $CH_2^{80}Br^{\cdot}$ radical and a possible explanation is that it is formed in a sequence of unimolecular reactions (equation 76):

$$(c\text{-}C_3H_5^{80}Br)^{**} \xrightarrow{A} (CH_2{=}CHCH_2^{80}Br)^* \xrightarrow{B} CH_2{=}\dot{C}H + \dot{C}H_2^{80}Br \tag{76}$$

The collision with the surrounding molecules is enough to stabilize the excited allyl bromide and to inhibit reaction B but not reaction A. If this mechanism is correct equations 77 and 78 are the competitive reactions

$$(CH_2{=}CHCH_2^{80}Br)^* \xrightarrow{k_1[M]} CH_2{=}CHCH_2^{80}Br \tag{77}$$

$$(CH_2{=}CHCH_2^{80}Br)^* \xrightarrow{k_2} CH_2^{80}Br^{\cdot} + C_2H_3 \tag{78}$$

and the ratio of the yields $[CH_2{=}CHCH_2^{80}Br]/[CH_2^{80}Br^{\cdot}]$ should equal $k_1[M]/k_2$, i.e. it should be proportional to the total pressure as was really found[77]. However, Saeki and Tachikawa pointed out[77] that excited allyl bromide has another path for decomposition, by breaking the weaker C–Br bond (equation 79):

$$(CH_2{=}CHCH_2^{80}Br)^* \xrightarrow{k_3} CH_2{=}C\dot{H}CH_2 + {}^{80m}Br \tag{79}$$

This step cannot be followed up since it does not lead to radioactive organic products. However, the fact that the sum of $CH_2{=}CHCH_2^{80}Br$ and $\dot{C}H_2^{80}Br$ is almost independent of the pressure indicates that this last step is of small improrttance in the case of ^{80}Br + cyclopropane. This step, however, is important in the case of ^{80}Br + cyclopropyl bromide. For ^{80}Br + cyclopropyl bromide Saeki and Tachikawa found that the increase of total pressure led also to a decrease in the yield of $\dot{C}H_2^{80}Br$ and increase in the yield of $CH_2{=}CHCH_2^{80}Br$[77]. However, while the yield of $CH_2^{80}Br$ decreased from 3.1 % to 2.1 % (when the pressure was changed from 1.37 to 13.4 kPa), the yield of $CH_2{=}CHCH_2Br$ increased from 3.0 to 12.3 %. The difference between the decomposition of $c\text{-}C_3H_5^{80}Br$ formed by either ^{80}Br for H reaction or ^{80}Br for Br reaction was explained by Saeki and Tachikawa as due to the higher energy (above 4 eV) left in the molecule in the ^{80}Br-for-H reaction which

enables reaction 78 to occur while in the case of ^{80}Br-for-Br substitution, the allyl bromide formed did not have enough energy (only between 2 and 4 eV) to break the C–C bond. A question left unanswered is why the excited allyl bromide formed by ^{80}Br-for-H exchange decomposed only by the more endothermic process (reaction 78) and there is only very little, if at all, decomposition by reaction 79.

Similarly to the contradiction about the observation of c-$C_3H_5{}^{80}Br$ in the reaction of ^{80}Br + cyclopropane which Saeki and Tachikawa observed while Wai and Jennings could not find it, there is also a disagreement about its formation in the reaction of ^{80}Br + cyclopropyl bromide. Saeki and Tachikawa[77] found its yield to be 0.4% independent of the total pressure (1.4–13.4 kPa) while Su and Tang[65] did not find any ^{80}Br–cyclopropyl bromide at 107 kPa (composed mainly of Ar). This last discrepancy may be due to the different energy of the hot atom since the Saeki and Tachikawa hot atom was formed by (n, γ) reaction leading to higher energy than the isomeric transition used by Su and Tang.

The ^{80}Br–allyl bromide formed in the reaction ^{80}Br + c-C_3H_6 can be formed not only by the structural isomerization of excited c-$C_3H_5^{80}Br$ but also by ring-opening (equations 80 and 81):

$$^{80}Br^* + c\text{-}C_3H_6 \rightarrow \dot{C}H_2CH_2CH_2{}^{80}Br \tag{80}$$

$$\dot{C}H_2CH_2CH_2^{80}Br \rightarrow CH_2{=}CHCH_2^{80}Br + H \tag{81}$$

However, it may be expected that the bromopropyl radical will react mainly by routes different than 81, i.e. either by breaking of the C–C bond (equation 82), the activation energy for which is 27–37 kcal mol^{-1} (compared to 47–52 kcal mol^{-1} for the C–H bond)

$$\dot{C}H_2CH_2CH_2^{80}Br \rightarrow CH_2{=}CH_2 + \dot{C}H_2^{80}Br \tag{82}$$

or by reacting with the scavenger, Br_2 or I_2 (equation 83):

$$\dot{C}H_2CH_2CH_2^{80}Br \xrightarrow{Br_2} BrCH_2CH_2CH_2^{80}Br \tag{83}$$

The yield of $BrCH_2CH_2CH_2^{80}Br$ found experimentally in bromine-scavenged cyclopropane is less than 1% of the $\dot{C}H_2^{80}Br$ yield. Thus ring-opening has some influence on this system but not to any significant extent.

De Jong and coworkers[78] studied the reaction of ^{76}Br and ^{77}Br, formed by β^+ and electron capture from ^{76}Kr and ^{77}Kr respectively, with cyclopropane. There are three differences between ^{76}Br and ^{77}Br. The first one is that ^{76}Br is formed mainly through electron capture (99.7%) and only 0.3% by β^+-decay, while ^{77}Br is formed 84% by β^+-decay and 16% by an electron capture process[81,82]. The second difference is that the maximum recoil energy for ^{76}Br is 7.2 eV while for ^{77}Br, it is 57 eV for the EC process and 36 eV for β^+. The third difference is the charge of the recoil atom. For ^{76}Br it is 100% positive charge (+1 to +13) whereas the ^{77}Br is 35% positively charged (+1 to +13), 15% neutral and 50% negatively charged[80].

The reaction of hot^{76,77}Br with cyclopropane was found to lead to methyl bromide, ethyl bromide, vinyl bromide and cyclopropyl bromide together with high boiling polymeric products which were not eluted from the chromatographic column (12–40% for ^{76}Br and 6–20% for ^{77}Br). H_2S was used to scavenge thermal species, due to its readily attackable H atoms, and only the high CH_3Br yield was found to decrease upon addition of H_2S. Moderation with 95% neon decreases considerably the yield of the high boiling point products (6–12% and 3–4% for ^{76}Br and ^{77}Br, respectively). The addition of 95% Ne in the case of ^{76}Br decreases only the yield of cyclopropyl bromide by a factor of 9.4 for ^{76}Br or 16 for ^{77}Br whereas the ethyl bromide yield decreased by a factor of 2.4 and those of methyl bromide, vinyl bromide and allyl bromide decreased by factors of 1.4, 1.1 and 1.2, respectively. This indicates that only cyclopropyl bromide was formed by a reaction of a

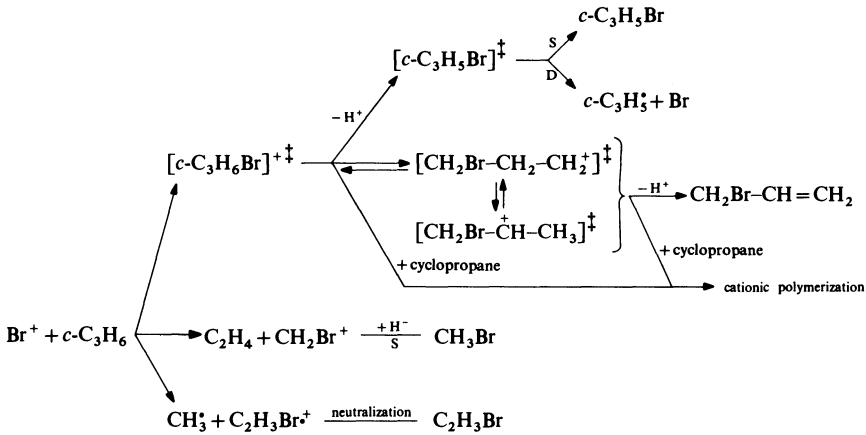
hot species. The much lower yield of $c\text{-}C_3H_5Br$ still formed in the highly moderated system is either due to some of the atoms reacting before being moderated by Ne, or as De Jong and coworkers suggested[78], due to Br^+ ions (equation 84):

$$\begin{aligned} Br^+ + c\text{-}C_3H_6 &\rightarrow (c\text{-}C_3H_6Br^+)^* \\ (c\text{-}C_3H_6Br^+)^* + c\text{-}C_3H_6 &\rightarrow c\text{-}C_3H_5Br + i\text{-}C_3H_7^+ \end{aligned} \tag{84}$$

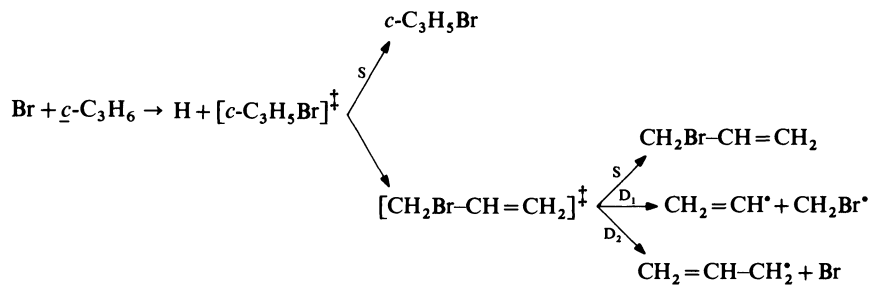
The enthalpy of the overall process is -4.6 eV.

Increasing the pressure of the cyclopropane (in a system with H_2S as a scavenger and without moderator) leads to an increase in the yield of $c\text{-}C_3H_5^{76,77}Br$ which is followed by decrease in the yield of $CH_3^{77}Br$ and $C_2H_5^{77}Br$. In the case of ^{76}Br there is no decrease in any organic product with increasing pressure, indicating that the decomposition of the excited parent molecule leads to inorganic bromide.

De Jong and coworkers believe that ^{76}Br reacts only as ions[78]. The decrease in the yield of $c\text{-}C_3H_5Br$ at high pressure of neon is ascribed to the low proton affinity of neon and to the low concentration of suitable proton acceptors (H_2S or cyclopropane) which makes proton transfer from $(c\text{-}C_3H_6Br^+)$ less likely in a moderated system. The longer lifetime of this ion enables a larger fraction of this ion to be isomerized to the more stable non-cyclic $C_3H_6Br^+$ which may later be polymerized. The sequences of reactions of hot $^{77}Br^+$ and ^{77}Br as suggested by De Jong and coworkers are given in Schemes 1 and 2, where S means stabilization, D means decomposition and I stands for isomerization.



SCHEME 1



SCHEME 2

6. The reaction of hot iodine atom with cyclopropane

Certout and Schleifer[83] studied the reaction of ^{125}I, produced from the electron capture decay of ^{125}Xe, in gaseous cyclopropane. In the presence of very low concentrations of I_2 as a scavenger, very high yields of organic products, about 80%, are obtained. On increasing the O_2 scavenger concentration, the yield decreases until it reaches a plateau and for 4×10^{-4} to 4×10^{-2} molar fraction of I_2 the organic yield is about 9.5% (CH_3I, 0.20%; $CH_2=CHI$, traces; C_2H_5I, 0.05%; n-C_3H_7I, 8.55% and n-$C_5H_{11}I$, 0.70%). Besides I_2 as a scavenger of radicals and ions, they studied the effect of oxygen as a radical scavenger and CS_2 as an electrons scavenger. The distribution of ^{125}I between the various organic iodides is given in Table 9.

^{125}I formed by the electron capture of ^{125}Xe has a mean primary charge of +8 to +9[84] and energies up to 4.4 eV, resulting from neutrino recoil[85].

The effect of the electron scavenger, CS_2, is explained as due to preventing the neutralization of the cations in the system and subsequent reaction of ^{125}I in the ^3P state with cyclopropane or with the radiolytic products of the substrate. In the presence of CS_2 the major product is methyl iodide similarly to the major product of $^{76,77}Br$ found by De Jong and coworkers[78]. However the analog to the main product in the case of I_2 or O_2 as scavenger, namely, n-propyl bromide was not found at all by De Jong and coworkers. They found the second and third major products to be allyl bromide and cyclopropyl bromide while Certout and Schleifer[83] did not find the respective iodides at all. It is not clear if this is due to the difference between Br and I or due to the different amount of radiolysis induced by each of them.

Certout and Schleifer suggested Scheme 3 to explain their results.:

$$^{125}I^* + c\text{-}C_3H_6 \rightarrow {}^{125}IC_nH_m + C_{3-n}H_{6-m}$$
$$^{125}I^+ + c\text{-}C_3H_6 \rightarrow {}^{125}I + c\text{-}C_3H_6^+$$
$$c\text{-}C_3H_6^+ + c\text{-}C_3H_6 \rightarrow \dot{C}_3H_7^+ + \dot{C}_3H_5$$
$$c\text{-}C_3H_6^+ \rightarrow \dot{C}H_2CH_2\,\dot{C}H_2^+$$
$$^{125}I + \dot{C}_3H_7^+ \rightarrow {}^{125}IC_3H_7^+$$
$$^{125}I + \dot{C}_3H_5 \rightarrow {}^{125}IC_3H_5$$
$$^{125}I + \dot{C}H_2CH_2\,\dot{C}H_2^+ \rightarrow {}^{125}I\,\dot{C}_3H_6^+$$
$$^{125}IC_3H_6^+ + c\text{-}C_3H_6 \rightarrow {}^{125}IC_3H_7 + c\text{-}C_3H_5^+$$
$$^{125}IC_3H_7^+ + I_2 \rightarrow {}^{125}IC_3H_7 + I_2^+$$
$$^{125}IC_3H_7^+ + c\text{-}C_3H_6 \rightarrow {}^{125}IC_3H_7 + c\text{-}C_3H_6^+$$

SCHEME 3

In the presence of oxygen ^{125}I reacts with O_2 to give IO_2 which subsequently reacts (equation 85):

$$^{125}IO_2 + R^+ \rightarrow R^{125}I^+ + O_2 \qquad (85)$$

C. Condensed Phase (Liquid and Solid)

1. The reaction of hot bromine atom with liquid cyclopropyl bromide

Wai and Jennings[76] studied the yield of the various organic products in the reaction of ^{80m}Br produced by (n, γ) reaction with liquid c-C_3H_5Br in the presence of I_2 as a scavenger.

TABLE 9. Distribution of ^{125}I (in percent of the total organic yield) in organic iodides for the reaction of ^{125}I (electron capture induced) with gaseous cyclopropane

Product \ Scavenger	I_2	O_2	CS_2
CH_3I	2	traces	55
CH_2=CHI	traces	2.5	1
C_2H_5I	0.5	2.5	15
n-C_3H_7I	90	91.8	24
i-C_3H_7I	—	—	5
n-$C_5H_{11}I$	7.5	3.2	traces

The products found were methyl bromide (1.0%), vinyl bromide (0.6%), allyl bromide (12.0%) and cyclopropyl bromide (2.3%). The sum of the yields of allyl bromide and cyclopropyl bromide is about the same as in the gas phase, where no cyclopropyl bromide was found, indicating that in the liquid phase 15% of the excited ^{80m}Br-cyclopropyl bromide is stabilized and 85% isomerized to allyl bromide.

Saeki and Tachikawa[77] studied the reaction of ^{79}Br (n, γ) ^{80}Br with liquid cyclopropyl bromide also in the presence of I_2. They found an extra product $CH_2^{80}BrI$ formed from the reaction of the $\dot{C}H_2^{80}Br$ with the I_2 scavenger. While this is the main product for low pressure gaseous cyclopropyl bromide and the second major product for higher pressure gas phase it is only the fifth in the liquid phase. The distribution of ^{80}Br between the organic products is different from that found for ^{80m}Br by Wai and Jennings[76] as can be seen in Table 10. This table includes also the results of Su and Tang[65] which use ^{82m}Br(I.T) ^{82}Br at $-78°C$. It can be said that in the liquid phase 14–25% from the excited c-C_3H_5Br is stabilized. There is no apparent reason for the difference of the results of Wai and Jennings[76] compared to those of Saeki and Tachikawa[77]. As in the reaction in the gas phase there is no mention of formation of 1- and 2-bromopropenes, and it is not clear if they are not formed at all in the isomerization or if their formation was not studied.

TABLE 10. Distribution of hot bromine in the I_2 scavenged reaction with liquid cyclopropyl bromide

Product	^{80m}Br(RT)[76]	^{80}Br(RT)[77]	^{82}Br ($-78°C$)
CH_3Br	0.06	0.10	0.07
CH_2=CHBr	0.04	0.08	0.04
CH_2=$CHCH_2Br$	0.76	0.52	0.65
c-C_3H_5Br	0.14	0.25	0.14
$\dot{C}H_2Br$	—	0.05	0.09

RT = room temperature.

2. *The reaction of electron capture induced ^{76,77}Br with solid cyclopropane*

Frost and coworkers[86] allow bromine atoms formed by the systems $^{76}Kr \xrightarrow{EC} {}^{76}Br$ and $^{77}Kr \xrightarrow{EC} {}^{77}Br$ to react with cyclopropane in the solid phase at 77 K. In contrast to the reaction of the same atoms in the gaseous phase where De Jong and coworkers[78] found the major product to be methyl bromide, in the solid phase the major product is isopropyl bromide. Table 11 gives the yield of the various products in both gas and solid phases. The

TABLE 11. Yields (%) of brominated products from the decay of $^{76,77}Br$ in cyclopropane

Product	Gaseous phase[78]			Solid phase[84]		
	^{76}Br	^{77}Br	$^{76}Br/^{77}Br$	^{76}Br	^{77}Br	$^{76}Br/^{77}Br$
CH_3Br	0.97	1.4	0.69	1.2	0.5	0.42
C_2H_5Br	0.12	0.30	0.40	15.4	11.4	1.35
C_2H_3Br	0.33	0.35	0.94	< 0.02	< 0.02	
$CH_2{=}CHCH_2Br$	0.58	0.47	1.23	*a*	*a*	
c-C_3H_5Br	0.47	0.79	0.59	2.7	1.7	2.6
i-C_3H_7Br	*a*	*a*		23.3	19.4	1.2
C_4H_9Br	*a*	*a*		5.1	2.6	2.0
$C_5H_{11}Br$	*a*	*a*		2.0	1.0	2.0
$C_6H_{13}Br$	*a*	*a*		1.8	0.7	2.6

[a] Yield not mentioned in the paper.

total organic yield in the solid phase is more than one order of magnitude higher than in the gas phase. This indicates that caging reactions are predominantly responsible for the observed product distribution in the solid phase. An important observation is that individual product yields are different for ^{76}Br and ^{77}Br and that the $^{76}Br/^{77}Br$ yield ratio varies from product to product. This variation in the $^{76}Br/^{77}Br$ yield ratio is due to the difference in the recoil energy and the charge state. The fact that the major product in the solid phase is isopropyl bromide and not propyl bromide shows that this product is not formed by ring-opening but by the reaction of bromine with isopropyl radical or ion, formed by radiolysis of cyclopropane.

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CHAPTER 15

Electrochemistry of the cyclopropyl group

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I. INTRODUCTION

This chapter describes the electrochemical formation of the cyclopropyl ring both in fused and non-fused systems, by anodic and cathodic processes. The electrochemical properties of cationic cyclopropyl and cyclopropenyl derivatives are surveyed, as well as those of related compounds such as bicyclobutanes, cyclopropanones, cyclopropanols, cyclopropenones, etc. All quoted electrochemical potentials are related to SCE and corrected

accordingly whenever a different reference electrode was cited. The present review covers the literature cited in *Chemical Abstracts* up to mid-January, 1985. The following abbreviations are used for the electrolytes in this chapter: TEAP, tetraethylammonium perchlorate; TEAB, tetraethylammonium bromide; TBACl, tetrabutylammonium chloride; TBAB, tetrabutylammonium bromide; TBAF, tetrabutylammonium fluoroborate; TEAF, tetraethylammonium fluoroborate; TEAI, tetraethylammonium iodide; $TBAFP_6$, tetrabutylammonium hexafluorophosphate; Et_4NOTs, tetraethylammonium tosylate.

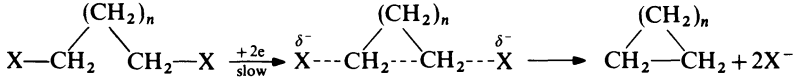
II. ELECTROCHEMICAL FORMATION OF THE CYCLOPROPYL RING

A. Cathodic Reductive Cyclization

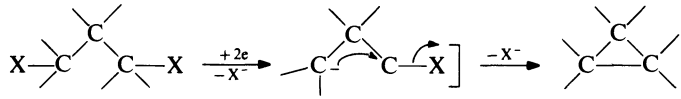
1. 1,3-Dihalo aliphatic compounds

One of the most common electrochemical ways to form a cyclopropyl ring is by the cathodic reduction of organic 1,3-dihalides. In general, the electroreduction of organohalogen derivatives may lead to diverse processes resulting in the conversion of the carbon–halogen bond to a carbon–hydrogen, a carbon–carbon or a carbon–metal bond. The first electrochemical step involves an electron transfer from the electrode to the substrate to form anion radicals $[RX]^{\cdot-}$, whose lifetime may vary from, e.g., 3×10^{-9} s to 5 s. The stability and fate of $[RX]^{\cdot-}$ depend on various factors which are discussed in detail in recent reviews[1,2].

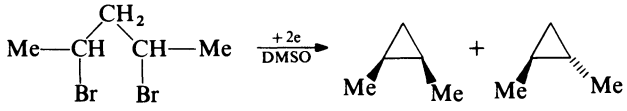
It has been initially proposed[3,4] that the electrochemical formation of cycloalkanes from α,ω-dihaloalkanes involves a concerted mechanism in which a two-electron cleavage of one C–X bond to form a carbanion takes place simultaneously with the displacement of the second halogen. Later, Fry and Britton[5] questioned this mechanism and suggested a



stepwise process involving a rapid cyclization by an initially formed carbanion intermediate: This explanation is based on the observation that the electrochemical reduction



of stereoisomeric 2,4-dibromopentanes in DMSO yielded in each case a mixture of roughly equal amounts of *cis*- and *trans*-1,2-dimethylcyclopropanes. However, Wiberg



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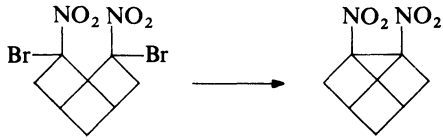
and Epling[6] pointed out that although the stepwise explanation is plausible it need not be true for all 1,3-dihalides, and certainly not under all conditions. For instance, the cyclic voltammogram of 1,3-dibromopropane in DMF shows two irreversible waves. When a preparative scale reduction was carried out at a relatively high potential (−2.65 V, at Pt)

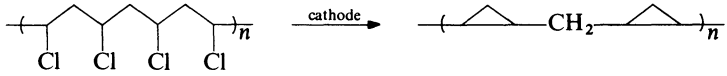
the major product (91 %) was cyclopropane in addition to propane (9 %). At less negative potentials the ratio of propane to cyclopropane had increased, and at −1.45 V 86 % of propane and 14 % of cyclopropane were formed. Furthermore, when the electrolysis was carried out in the presence of a deuterium donor the formed propane contained 8.8 % deuterium, indicating the occurrence of some hydrogen atom transfer. The authors concluded that dibromides may be reduced to a free radical via a one-electron process and that a mechanistic change may take place at more negative potentials, leading to a direct two-electron reduction which forms the ring in one step. Furthermore, it has been found[6, 7a] that structural changes can drastically change the reduction behavior in cyclic voltammetry. For example, unlike 1,3-dibromopropane, the reduction of 2,4-dibromopentane does not show two resolved reduction waves.

Table 1 lists the experimental conditions for the electrochemical formation of a cyclopropyl ring from a variety of 1,3-dihaloalkanes, mostly from dibromoalkyl derivatives. A 'free' cyclopropyl ring as well as a spiro derivative (entry 6), bicyclobutanes (entries 8–10) and other fused and highly strained systems such as tricyclene (entry 11) and a propellane derivative (entries 12, 13) were obtained. In addition, Carroll and Peters[16] have found evidence for the intermediacy of [2.2.1]propellane upon reducing 1,4-dihalonorbornanes electrochemically at a low temperature, although attempts to isolate it were unsuccessful. The intramolecular electrochemical reduction of a dihalo-substituted tricyclic compound leads to cyclization with formation of a tetracyclic derivative in which

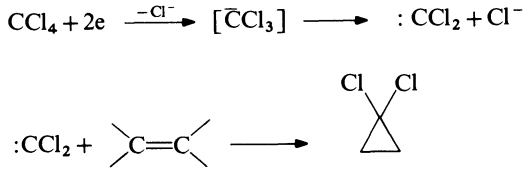


one of the rings is a cyclopropyl ring[13]. Interestingly, the formation of cyclopropene (entry 14) and a cyclopropanone[9] derivatives have been also reported, although the latter was only characterized spectroscopically but has not been isolated.

It is noteworthy that the reduction of organic halides can also be used for the modification of polymers[7b]. In general, gem-dihalides are reduced in a stepwise manner

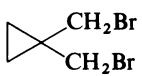
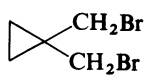
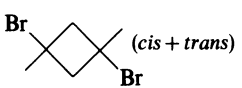
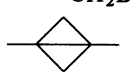
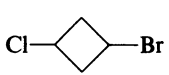


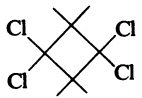
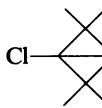
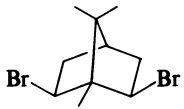
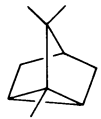
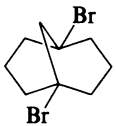
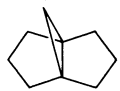
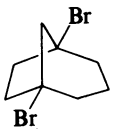
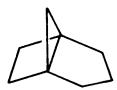
which affects the replacement of halogens with hydrogens[17–19]. However, in certain cases[17] carbenes were trapped by olefins to form dihalocyclopropanes. In an extensive



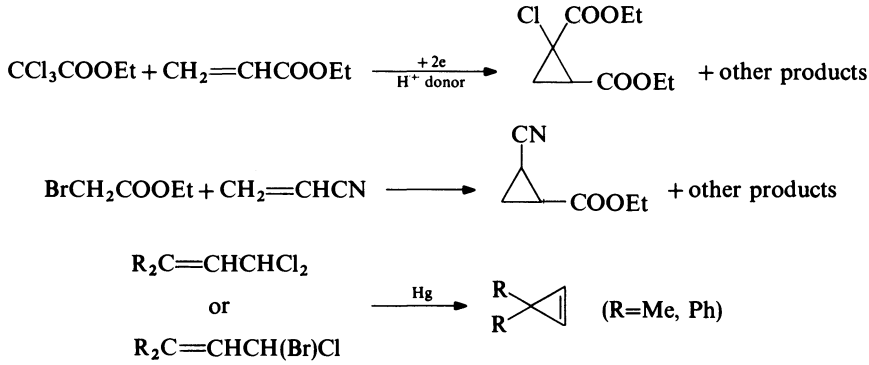
study Baizer and Chruma[20] obtained substituted cyclopropanes by reducing several halo compounds in the presence of various Michael acceptor olefins. Doupeux and Simonet[15] obtained cyclopropenes by reducing the 3,3-dichloro- or the 3-bromo-3-chloro-propenes. However, the corresponding 3,3-dibromopropenes did not yield cyclopropenes but were reduced to the propenes $R_2C=CHMe$.

TABLE 1. Formation of a cyclopropyl ring by electrochemical reduction of 1,3-dihalo organic compounds

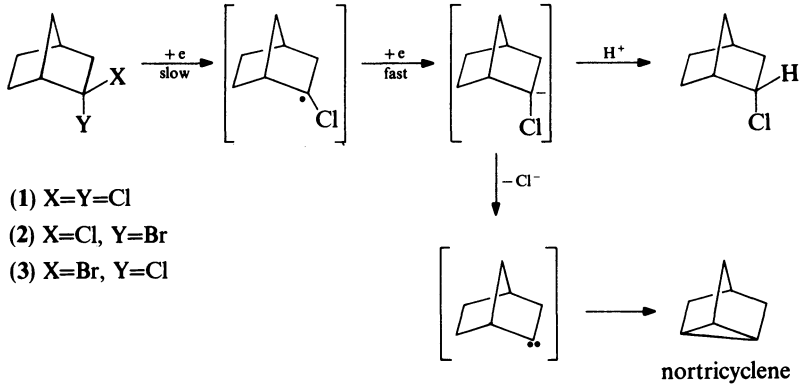
No.	compound	Cathode	E(V vs. SCE)[a]	Medium	3-Membered ring product (%)	Ref.
1	$Br(CH_2)_3Br$	Hg	−1.91	DMF, LiBr	Cyclopropane (> 85%)	3, 4
		Pt	−2.65	DMF, Et_4NBr	Cyclopropane (91%) + propane (9%)	6
		Pt	−1.45	DMF, Et_4NBr	Cyclopropane (14%) + propane (86%)[b]	6
2	$Cl(CH_2)_3Br$	Hg	−2.4	DMF, n-Bu_4NClO_4	Cyclopropane[c]	4
3	$MeCH(Br)CH_2CH(Br)Me$	Hg	−2.2	DMF or DMSO, Et_4NBr	 (41–44%) +  (40–45%) + others	5[d]
4	$BrCH_2CH(OH)CH_2Br$	Hg	−1.78	MeCN, Et_4NOTs	Hydroxycyclopropane (60%)	4, 8
5	$PhCH(Br)CH_2CH_2Br$	Hg	−0.9 to −1.4[e]	MeCN, Et_4NBr	Phenylcyclopropane (70%) + olefins	8
6		Hg	−2.3	DMF, n-Bu_4NClO_4	 (~ 40%)	9–11
7	$C(CH_2Br)_4$[f]	Hg	−1.8	DMF, n-Bu_4NClO_4	 (47–58%)	9–12
8	 (*cis* + *trans*)	Hg	−2.02	DMF, LiBr	 (55–94%)	3
9		Hg	−2.0	DMF, LiBr	 (60%) + others	3

10		Hg	−2.0	DMF, LiBr		*c*	3, 4
11		Hg	−2.48	DMF, Me_4NBr or 90% EtOH, n-Pr_4NClO_4		(~ 60%) + others	14
12		Pb or C	−0.6	H_2O–acetone, $LiClO_4$		(75–80%)	13
13		Hg	1.8–3.0 DC	DMF, LiBr		'High yield'	3, 4
14	$R_2C(Cl)CH=CHCl$	Hg	−1.2 to −1.75	DMF, TEAP		(R = Me, Ph)[c]	15

[a] *E* denotes either polarographic $E_{1/2}$, or peak potential E_p or controlled potential in large scale electrolysis.
[b] When the reaction was not carried out to completion, small amounts of 1-bromopropane were detected.
[c] No yield is specified.
[d] The range of yields stems form the nature of the stereoisomer (*dl* or *meso*) used. Other products involved *n*-butane, *cis*- and *trans*-2-butene and 1-butene.
[e] Constant current electrolysis with 1 A.
[f] Under uncontrolled potential electrolysis spiropentane, 2-methyl-1-butene and methylenecyclobutane rather than the dibromo derivative were formed.



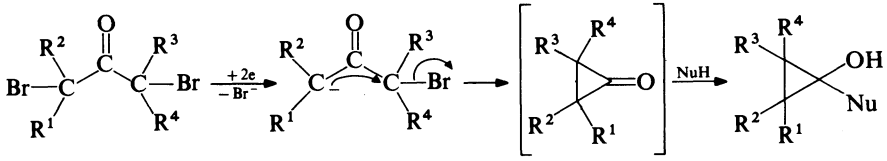
Fry and Reed[21] studied extensively the stereochemistry of the reduction of alkyl halides. As model compounds they chose 2,2-dichloronorbornane (**1**), 2-*exo*-chloro,2-*endo*-bromonorbornane (**2**) and 2-*exo*-bromo,2-*endo*-chloronorbornane (**3**) which were reduced in DMF-TEAB at -2.24 V, -1.63 V and -1.53 V (v. SCE), respectively. Under similar experimental conditions each of the dihalonorbornanes gave identical ratios of the same products, independent of the nature of the dihalide. This observation suggests that all three compounds are converted electrochemically to a common carbanionic intermediate. However, the relative proportion of the nortricyclene to *endo*-chloronorbornane formed from this intermediate was found to be highly dependent upon experimental conditions, such as the concentration and nature of proton donor present in solution, or the nature of the electrolyte. Under certain conditions the yield of the nortricyclene was up to 63%.



(**1**) X=Y=Cl
(**2**) X=Cl, Y=Br
(**3**) X=Br, Y=Cl

2. *Dihaloketones*

Initial attempts to prepare cyclopropanones by electrochemical reduction of dihaloketones were unsuccessful[22]. Fry and Scoggins[23] have shown later that tetramethylcyclopropanone and 2,2-dimethylcyclopropanone can be prepared as transient intermediates by electroreduction of the corresponding α,α'-dibromoketones. The highly reactive cyclopropanones were trapped by methanol as their hemiacetals (**4**, Nu = OMe) as is shown below. When the reduction was carried out at 0°C or below the cyclic products were obtained exclusively and in high yields ($\sim 90\%$). In the electroreduction[23] of 1,3-dibromo-3-



(4)

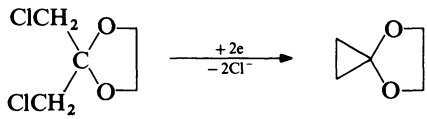
methyl-2-butanone in DMF in the absence of added nucleophile, the corresponding derivative was detected as a transient compound by infrared spectroscopy.

Tilborg and coworkers[24] recently reported an extensive study concerning the electrosynthesis of cyclopropanone adducts from either α,α'-dibromo ketones or from α,α'-dibromo- and α,α'-dichloro-carbonyl protected ketones. With the non-protected ketones the reductions were carried out in MeCN in the presence of various nucleophiles (Table 2). It was found that the yields of cyclopropanone adducts decrease when the dihaloketone becomes less substituted, due to a competing side reaction in which a bromide is displaced by the nucleophile. Furthermore, in the presence of excess of added protic nucleophile the yields of the cyclic products decrease due to a competing protonation of the anionic intermediate.

TABLE 2. Electrosynthesis of cyclopropanone adducts (4) from reduction of dibromoketones at −1.0 V in MeCN–TEAB at Hg[24]

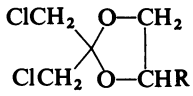
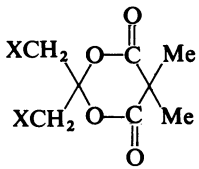
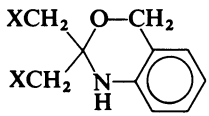
R^1	R^2	R^3	R^4	NuH	Temp. (°C)	Current yield (%)
Me	Me	Me	Me	MeOH	−5	50–80
				Me_2NH	−5	80
				$MeNH_2$	−20	60
				$PhNH_2$	−5	80
Me	Me	H	H	MeOH	−10	50
				Me_2NH	−20	30–70
Me	H	Me	H	MeOH	−10	30–50
				Me_2NH	−20	70
H	H	H	H	MeOH	−20	0
R^1–R^3 = $(CH_2)_7$, R^2 = R^4 = H				MeOH	−10	40

Carbonyl-protected acetals, acylals and aminals were used[24] in their reductive cyclization to form spiro derivatives of cyclopropanone. Good yields of the three-membered spiro compounds were obtained from the acetals while poor yields were obtained by using the acylals and aminals (Table 3). For example, however, the resulting cyclopropanone acetals

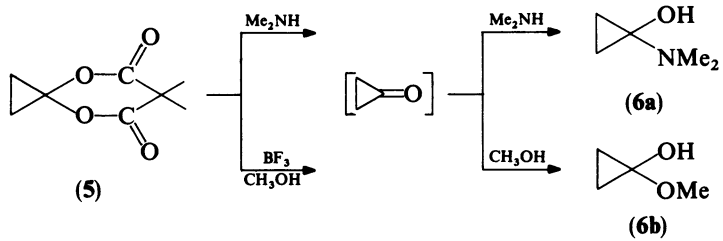


cannot be used as precursors for other cyclopropanone derivatives since their hydrolysis is generally accompanied by rupture of the cyclopropyl ring[25]. On the other hand, the

TABLE 3. Electrocyclization of 1,3-dihaloacetone derivatives in MeCN–TBACl at Hg cathode[24]

Starting material	Temp. (°C)	Potential (V vs. SCE)	Current yield (%) of spirocyclopropane product
			
R = H	0	−2.56	75
R = CH_2OH	−15	−2.76	70
			
X = Cl	−15	−2.00	0
X = Br	−20	−2.00	5
			
X = Cl	0	−2.70	10
X = Br	−10	−2.40	0

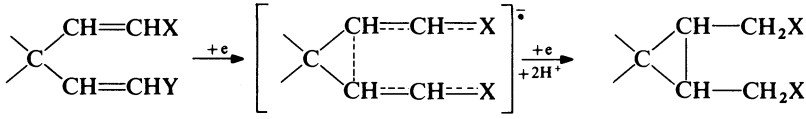
cyclopropane acylal (**5**) was found to be a good precursor for cyclopropanone and its derivatives **6a** and **6b**.



(**5**) (**6a**) (**6b**)

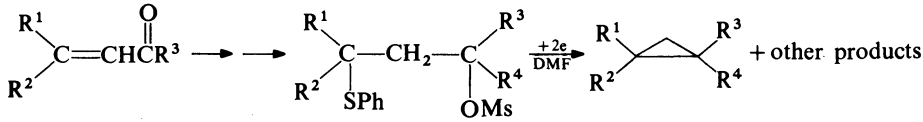
3. *Activated olefins*

Bis-activated olefins undergo electrohydrocyclization (EHC) by intramolecular reductive coupling. It was proposed[26] that the mechanism involves a concerted electron transfer and cyclization which generally gives a mixture of the *cis* and *trans* isomers of the cyclic product (**7**). The latter product is favored at low water concentration whereas at higher ones intermolecular radical–radical coupling competes[27].



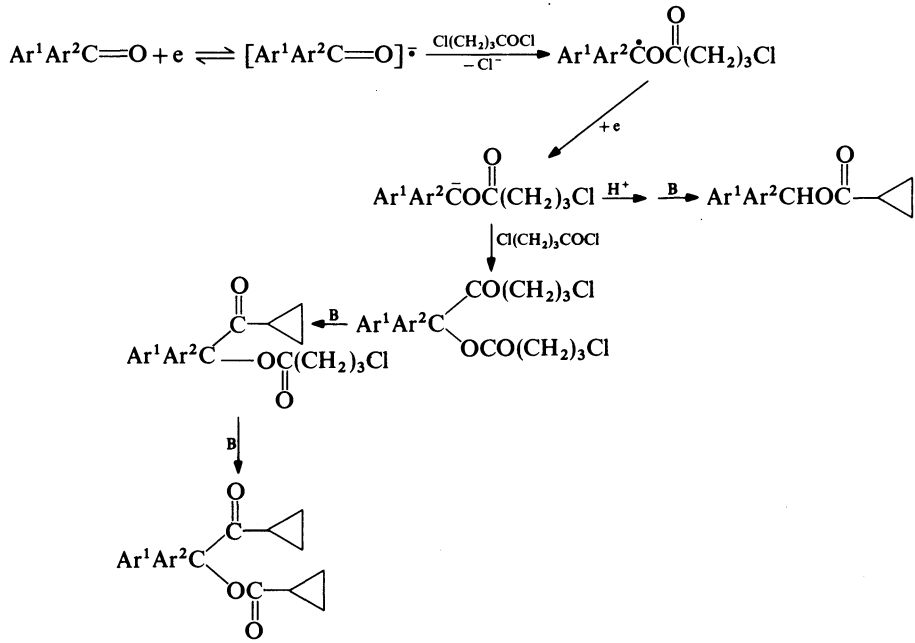
(7)

An example of an indirect formation of a cyclopropyl ring from an activated olefin was also reported[28]. A Michael addition of thiophenol to an α,β-unsaturated ketone followed by a chemical reduction (e.g. $NaBH_4$) yielded an alcohol which was converted to the methanesulfonate of the γ-phenylthioalcohol (**8**). When the latter is reduced electrochemically a cyclopropyl derivative is obtained.



(**8**) (major product, 74–94%)

Recently, Belot and coworkers[29] reported the electrosynthesis of mono- and dicyclopropyl carbonyl derivatives from the electrolysis of aromatic ketones and their corresponding Schiff bases in the presence of $X(CH_2)_3COCl$ (X = Br, Cl). Moderate yields, which depended on the solvent and other experimental conditions, were obtained.

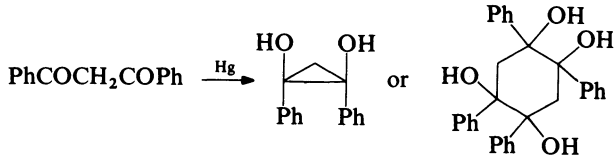


$Ar^1=Ar^2=Ph$
Ar^1Ar^2C=fluorenylidene
B=base

Reduction of a Schiff base derivative of benzophenone under similar conditions also yielded cyclopropyl products.

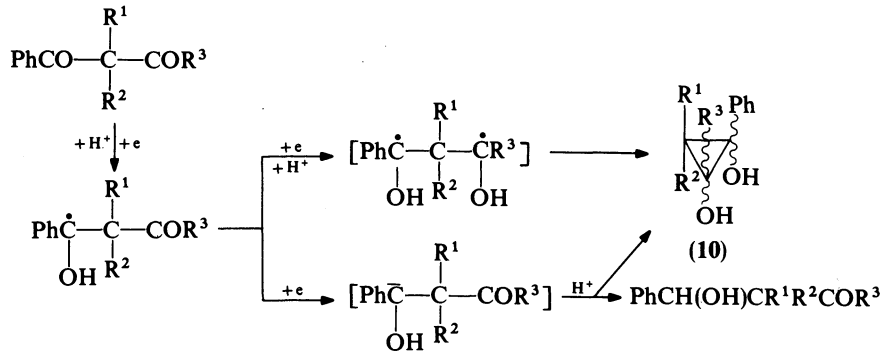
4. 1,3-Diketones

In 1967 Evans and Woodbury[30] reported a thorough electrochemical investigation of 1,3-diphenyl-1,3-propanedione in ethanol–water mixtures at a wide range of pH. Their polarographic and coulometric results imply formation of three different reduction products with the consumption of one, two and four electrons, respectively. A two-electron reduction of the substrate at pH = 7 leads possibly either to a 1,2-dihydroxycyclopropane (**9a**) or to 1,2,4,5-tetrahydroxycyclohexane derivative (**9b**) but the actual structure could not be determined absolutely due to difficulties in obtaining a pure product.



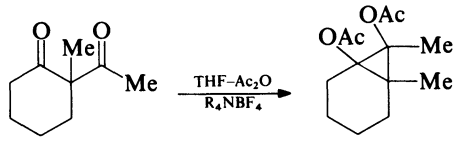
(**9a**) (**9b**)

Armand and Boulares[31] carried out an extensive study on the cathodic reduction of five 1,3-dione derivatives in 50% MeOH–H_2O at mercury (Table 4). Each dione exhibited one 2e-wave which was found to be pH dependent in the pH range 1–8, by being shifted cathodically in more basic solutions (−1 V to −1.5 V, respectively). It was found that the 2e polarographic wave corresponds to a reduction of the β-diketones to a 1,2-dihydroxycyclopropane (**10**). The following mechanism was suggested for the reduction in acidic or neutral protic media.

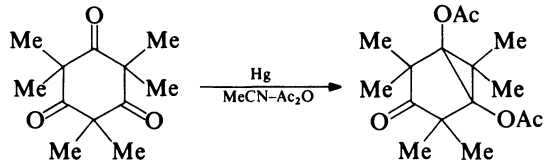


Other systems, involving β-diketones were also investigated and their reduction led to bicyclic products. For example, a 1,2-cyclopropanediol derivative (**12**) was isolated[32] as its diacetate from the electrolysis of (**11**).

The trione **13** behaved similarly. For comparison, reduction of **13** with 2 equivalents of Li in THF followed by treatment with acetyl chloride, afforded[33] the same product in 50%

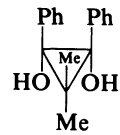
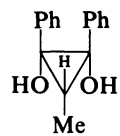
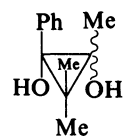
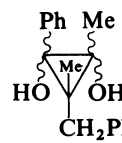


(11) (12) (33%)

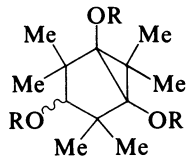


(13) (71%)

TABLE 4. Electrochemical reduction of $PhCOCR^1R^2COR^3$ in 1:1 MeOH–H_2O at mercury cathode[31]

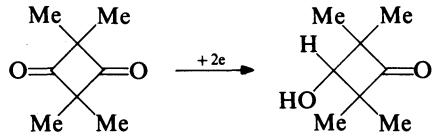
R^1	R^2	R^3	$E_{1/2}$(V) (pH)	Products (yield, %)	Comments
Me	Me	Ph	−1.25 (3.7)	 (80%)	Only one isomer was found
H	Me	Ph	−1.25 (3.7)	 (80%)	Only one isomer was found
H	Me	Me	−1.18 (3.8)		No large scale electrolysis was reported
Me	Me	Me	−1.15 (3.7)	 (80%)	Two isomers in a 1:1 ratio
Me	CH_2Ph	Me	−1.16 (3.7)		Yield was not reported. A mixture of isomers was formed

yield. When large excess of Li was used a trihydroxybicyclic product (R = H) was formed in 65–95% yield, which upon treatment with acetyl chloride gave the corresponding triacetate derivative (R = Ac).



R = H, Ac

The electrochemical reduction[7c] of 1,1,3,3-tetramethylcyclobutanedione (**14**) exhibits two one-electron waves in DMF. Macroscale electrolysis at the plateau of its second wave afforded the keto-alcohol **15** and not the bicyclobutane derivative.

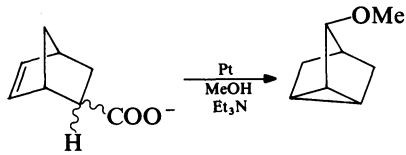


(**14**) (**15**)

B. Anodic Oxidative Cyclization

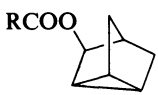
1. Carboxylic acids

Corey and coworkers[106] suggested that when the reactant in the Kolbé reaction is such that the R group will form a relatively stable carbocation, products other than Kolbé dimers (RR) or monomers (RH) may be formed by an additional electrochemical step. To test this idea they oxidized compounds which can generate stable carbocations. For instance, the electrolysis of either *exo*- or *endo*-5-norbornene-2-carboxylate (**16**) in methanol gave 3-methoxynortricyclene (**17**) in 50% yield.

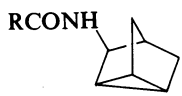


(**16**) (**17**)

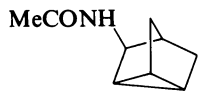
Laurent and coworkers[34] oxidized **16** in acetonitrile at Pt anode and characterized four cycloproopyl derivatives (**18**–**21**), among other products.



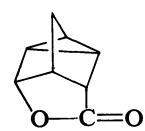
(**18**) (10%)



(**19**) (5%)



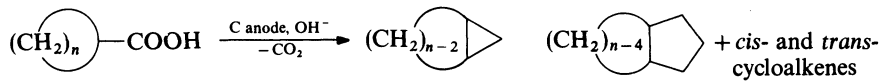
(**20**) (35%)



(**21**) (20%)

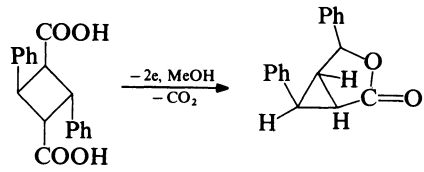
(R = 5-norbornenyl radical)

Traynham and coworkers[35, 36] studied the anodic oxidation of medium-ring (7–10 carbon atoms) cycloalkanecarboxylic acids which yielded bicyclic products (**22**, **23**), among others, due to transannular elimination.



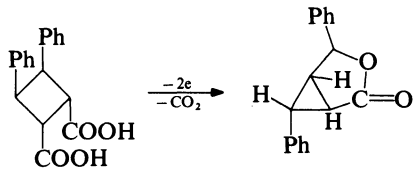
(**22**) (**23**)

Vellturno and Griffin[37] have used anodic decarboxylation as a preparative route to small ring compounds. Electrolysis of α-truxilic acid (**24**) produced the *cis*-lactone (**25**) as

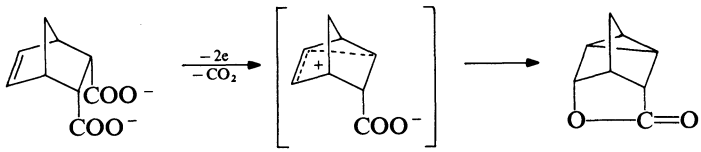


(**24**) (**25**)

the major product. Similarly, Paudler and coworkers[38] have shown that the *trans*-lactone was produced from β-truxinic acid. The anodic oxidation of dicarboxylates is now held

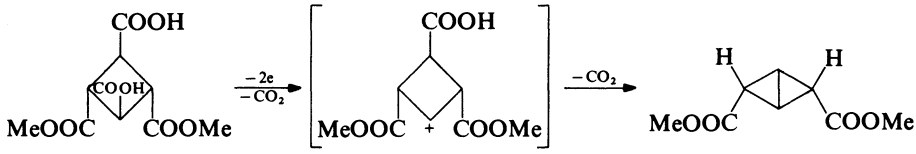


to be a two-electron oxidation rather than a concerted one-electron oxidation of both carboxylate groups, as shown below[39]:

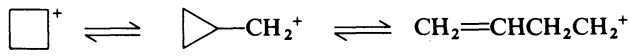


Electrolysis[37] of *trans,trans,trans*-1,3-dicarboxy-2,4-dicarbomethoxycyclobutane (**26**) produced the highly strained bicyclic compounds **27** and **28**, in 15% and 2%, respectively. The mechanism is uncertain although the following one was suggested[38]. Product **28** was also obtained from the bis-decarboxylation of 1,3-dicarboxypentane in methanol[37].

Keating and Skell[40] and later Laurent and Thomalla[41] have found that a similar mixture of products was obtained in the anodic oxidation of either cyclobutanecarboxylic acid, allylacetic or cyclopropaneacetic acid. They accounted for these results by a rapid equilibria among the carbocations initially formed. A similar observation is that in the anodic oxidation of the corresponding iodo reactants in acetonitrile *N*-(cyclopropylmethyl)acetamide was found in each product mixture[42]. It is noteworthy that the same identity in products also holds for the chemical reactions of solvolysis and



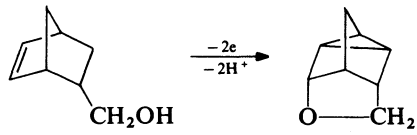
(26) (27) + (28)



deamination[43]. However, when bromocyclobutane was electrochemically oxidized in acetonitrile no cyclopropyl derivative was observed[44].

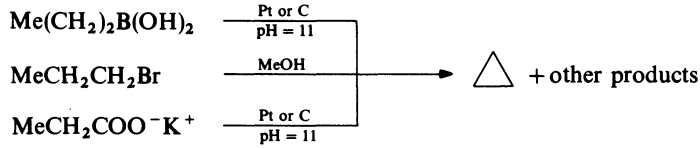
2. *Miscellaneous oxidations*

The previous sections surveyed the general electrochemical methods for producing a cyclopropyl ring in a variety of organic systems. In addition to those, more specific methods have appeared occasionally in the literature. Shono and coworkers[45] studied the anodic oxidation of 2-*endo*-5-norbornen-2-yl-methanol (**29**) in three different solvents. Among other products they obtained the tetracyclic system **30** where one of the rings is a cyclopropyl.

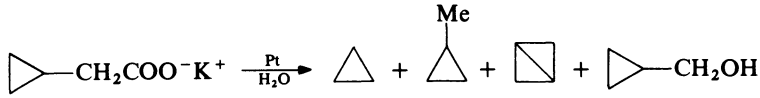


(**29**) (**30**) 13.8% in MeCN
22.3% in MeOH
6% in AcOH

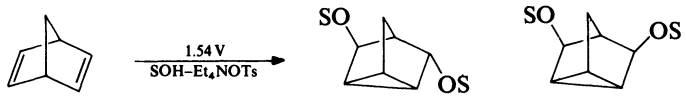
In some mechanistic studies, cyclopropane was formed by anodic oxidation of various substrates[46,47]:



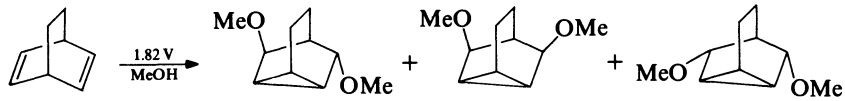
Keating and Skell[40] also reported the formation of cyclopropane, methylcylopropane, bicyclobutane and other products from the anodic oxidation of cyclopropylacetic acid. Rifi[3] obtained cyclopropane exclusively upon electrochemical reduction of $[Br(CH_2)_3\overset{+}{N}Et_3]Br^-$ at −1.34 V.



Intramolecular coupling between non-conjugated double bonds suitably disposed for transannular reaction has been carried out anodically[48,49]. Both norbornadiene (**31**) and bicyclo[2.2.2]-2,5-octadiene (**32**) reacted to yield 35–40% of products containing a cyclopropyl ring:



(**31**) S = OMe: 14% 15%
S = OAc: 17% 18%



(**32**) 23% ~5% 9%

In macroscale 'paired electrochemical synthesis' it was found that a correct choice of reactor design[50] and good mixing conditions[51] favor the production of cyclopropane adduct over that of the dihydrodimers:

anode: $2I^- \xrightarrow{-2e} I_2$

cathode: $2CH_2{=}CHCOOMe \xrightarrow{+2e} (-CH_2-\bar{C}HCOOMe)_2$

bulk: $(-CH_2-\bar{C}HCOOMe)_2 + 2CH_2(COOEt)_2$

$$\downarrow$$

$$(-CH_2CH_2COOMe)_2 + 2\bar{C}H(COOEt)_2$$

$$(\mathbf{A}^-)$$

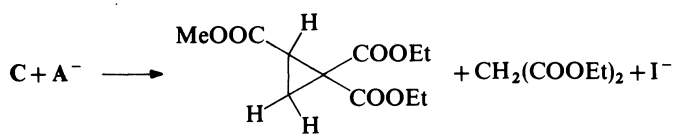
$$\mathbf{A}^- + CH_2{=}CHCOOMe \longrightarrow CH_2\bar{C}HCOOMe$$

$$CH(COOEt)_2$$

$$(\mathbf{B}^-)$$

$$\mathbf{B}^- + I_2 \longrightarrow \underset{\displaystyle CH(COOEt)_2}{\overset{\displaystyle CH_2CH(I)COOMe}{|}} + I^-$$

$$(\mathbf{C})$$

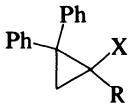


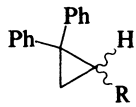
III. ELECTROCHEMICAL PROPERTIES OF CYCLOPROPYL DERIVATIVES

A. Cathodic Reduction of Cyclopropyl Halides

The electrochemical reduction of cyclopropyl halides has been widely investigated mainly in relation to its stereochemistry. No ring-opened products have been reported yet but substitution of the halogen by a hydrogen usually proceeds in high yields. Both monohalocyclopropanes, mostly bromide derivatives, and gem-dihalocyclopropanes were investigated. Several groups[52–54] have studied the stereochemistry of the electroreduction of optically active bromocyclopropanes and observed that the electrochemical stereospecificity can vary from 56% inversion to 100% retention (Table 5). In one case[54] the optically active (+)-1-bromo-1-methyl-2,2-diphenylcyclopropane was reduced both cathodically at Hg and chemically with either Li or Mg metal. The results revealed that the highest

TABLE 5. Electrochemical stereospecificity in the cathodic reduction of optically active cyclopropyl halides





X	R	E(vs. SCE)	Medium	Yield, %	% Stereospecificity	Ref.
Br	COOH	−1.1 to −1.2[a]	EtOH–TBAB–AcOH	86–96	26–35 inversion	52
Br	COO^-	−1.7[a]	EtOH–TEAB–OH^-	85–91	31–38 retention	52
Br	COOMe	−1.3 to −1.6[a]	EtOH–TBAB	73–95	30–56 inversion	52
Br	Me	−2.2[a]	EtOH–TEAB	73–80	21 retention	52
Br	Me	−2.68[b] (−0.94, −1.26)	MeCN–TEAB	62–92	63 retention[c]	53
I	Me	−1.96[b] (−0.94, −1.26)	MeCN–TEAB	54–75	55 retention	53
Br	$MeOCH_2$	−2.63[b] (−1.11, −1.47)	MeCN–TEAB	89.5	31.4 optical purity[d]	53
HgBr	Me	−2.25[b] (−0.30, −0.90)	MeCN–TEAB	35	100 retention[c]	53
Br	Me	−2.7		93	63 retention[c]	54
Br	COOMe[e]	−1.5	AcOH–NH_4OAc		70 retention	55
		−1.4			50 retention	55
		−1.3			31.5 retention	55
		−1.2			9.5 retention	55
Br	COOH[e]	−1.5	AcOH–NH_4OAc		52.5 retention	55
		−1.4			35 retention	55

[a] Effective potential at which material was electrolyzed at Hg.
[b] Peak potentials from cyclic voltammetry measurements at mercury-plated platinum, in MeCN–TEAB at 10 V s^{-1} sweep rate. Values in parentheses relate to peak potentials obtained when the potential was cycled in the positive direction after observation of the reduction.
[c] Electrolysis at −2.9 V. At −1.3 V only R_2Hg was formed.
[d] 2,2-Diphenyl(methylene)cyclopropane was obtained among other products.
[e] Only representative results are shown.

retention of configuration (63%) was obtained by the electrochemical reduction whereas only 45% and 13–18% retention was found with Li and Mg, respectively. However, the stereochemical results for some of the compounds[52] listed in Table 5 correspond closely with those observed in Zn metal reductions[55].

A French group[56] studied the stereochemical electroreduction of two bromocyclopropyl derivatives and found that the ease of cleavage of the C–Br bond depends on the nature of the supporting electrolyte cation which plays also an important role in the stereoselectivity of the reduction at Hg cathode. It was found that in aqueous acetic buffer the extent of a retention of configuration increased in the presence of NH_4^+ cations and at increasing negative working potentials. However, more inversion was found in the presence of R_4N^+ cations but it was independent of the working potential. The extent of inversion increased with the increase in the bulkiness of the organic cation.

With regard to the mechanism it was suggested[52] that an initial attack on the halogen side of the C–X bond by the electrode surface gives an electrode complex with the substrate, with the same configuration as the rectant. This is followed by a stereoselective reaction of the free (or electrode shielded) carbanion with the solvent or H^+. If the carbanion intermediate is configurationally stable during the time required to move away from the electrode (as would be expected for cyclopropyl carbanions which invert their configuration at a very low rate[57]) complete retention of configuration will be found. If the carbanion is not so stable and occasionally inverts before acquiring a proton from the medium a predominant but not exclusive retention will be observed. Either or both of these pathways lead to products with mainly retained configuration[58].

Recently Tallec and coworkers[59] investigated the stereochemistry of electroreductions of 1-substituted-2,2-diphenylcyclopropenyl bromides in aqueous media at various pHs and in the presence of strongly adsorbed alkaloids (Table 6). Their study shows that the existence of interaction between the alkyl bromides and nitrogen cations makes the two-electron cleavage of the C–X bond easier (sometimes by up to ~ 400 mV). In general, poor optical yields were obtained in the presence of each of the five alkaloids tested. However, the optical yield went up to 42% when the alkaloid inducer could act as a proton donor. It was also found that the alkaloids were efficient at low concentrations (10^{-4} to 5×10^{-4} M) indicating that the induction is a surface phenomenon.

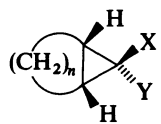
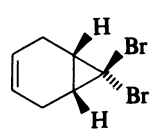
TABLE 6. Asymmetric electrochemical reduction of 1-X-2,2-diphenylcyclopropyl bromide[a] derivatives in the presence of strongly adsorbed alkaloids[b] as inducers[59]

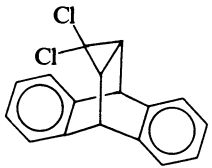
X	$E_{1/2}$ (V vs. SCE)	Medium	pH	Optical yield (%)
Br	−1.46	EtOH–H_2O (1:3)	4–10	Up to 42% (*R*-enantiomer)
COOMe	−1.06	EtOH–H_2O (1:1)	2–10	Up to 7.5% (*S*-enantiomer)
COOH	−1.06	EtOH–H_2O (1:1)	2–3	Up to 7.8% (*S*-enantiomer)
	−1.30	EtOH–H_2O (1:1)	4.7	Up to 4% (*S*-enantiomer)

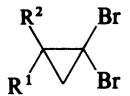
[a] There is no mention of the stereochemistry of these compounds in Ref. 59. The author of this chapter assumes that in each case a racemic mixture was reduced.
[b] Strychnine, brucine, emetine, yohimbine, methylstrychninium iodide, narcotine and sparteine.

The stereochemistry of electrochemical reduction of geminal dihalocyclopropanes shows clearly a preference for retention of configuration[58]. Stereochemical correlations between electrochemical (Hg) and Zn or Li/Hg reductions were found to hold for several geminal dihalocyclopropanes[58]. Most stereochemical results can be rationalized on the basis of attack on either halogen, although some investigators favor the mechanism in which the *endo* halogen is reduced preferentially with retention of configuration[60]. Table 7

TABLE 7. Electrochemical reduction of gem-dihalocyclopropanes

Compound	E (V vs. SCE)	Medium	Products ratio (*endo*) / (*exo*)		Ref.[a]
					
$n = 4$, X = Y = Br	−1.15	DMF–TEAB	1.2	1	60
	−1.15	AcOH–TEAB	4	1	60
	−1.26 ($E_{1/2}$)	DMF–LiCl	1.6	1	58
$n = 4$, X = Y = Cl	−2.05	DMF–LiCl	4.3	1	60
	−2.05	MeOH–5% HCl	19	1	60
		EtOH–TEAB	6	1	58
		DMF–TEAB	3.1	1	58
		EtOH–LiCl	~2	1	58
$n = 4$, X = Br, Y = Cl	−1.39 ($E_{1/2}$)	EtOH–LiCl	~1	1[b]	58
		EtOH–LiCl	1	2.6[b]	58
$n = 4$, X = Cl, Y = Br	−1.35 ($E_{1/2}$)	EtOH–LiCl	2.6	1[b]	58
		EtOH–TEAB	~3.6	1[b]	58
$n = 6$, X = Y = Br	−1.15	MeOH–5% HCl	1	0	60
	−1.15	MeOH–LiCl	2.7	1	60
	−1.15	MeOH–H_2O (9:1)	10.1	1	60

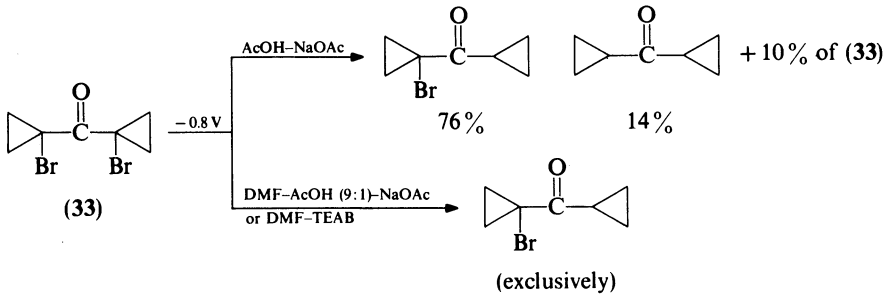
	Not specified	EtOH–TEAB	1	3.2	58

			Stereochemistry, % *cis* isomer[c]	
(+) or (−) R^1 = Ph, R^2 = COOH	−1.50	EtOH–H_2O (at diff. pH)	10	61
R^1 = H, R^2 = Ph	−1.30 ($E_{1/2}$)	pH = 2–10	62–84	62
R^1 = Me, R^2 = Ph	−1.34	pH = 4.7	50–82	62
R^1 = Me, R^2 = COOH	−1.27	pH = 4.7	65–85	62
R^1 = Me, R^2 = COOMe	−1.17	pH = 2–10	64–94	62
R^1 = Me, R^2 = COOEt	−1.18	pH = 2–10	56–99	62
R^1 = Ph, R^2 = COOH	−1.23	pH = 4.7	50–92	62
R^1 = Ph, R^2 = COOMe	−1.09	pH = 2–10	53–69	62
R^1 = Ph, R^2 = COOEt	−1.11	pH = 2–10	46–71	62

[a] Electrolyses in Ref. 60 were carried out at 0°C. All electrolyses were done on Hg cathode.
[b] In the electrochemical reduction of gem-bromochloropropyl derivatives the bromine is always substituted for hydrogen. Therefore Y = Cl in both
[c] *cis* Br and R^1.

summarizes the results of several groups who worked intensively on these systems and showed the effects of both the solvent and the nature of the halogen atom. The major product in most electrochemical reductions is the less stable *endo* isomer and in general its proportion increases in solvent of higher proton content.

Fry and Andersson[63] examined the electroreduction of over 50 α,α'-dibromoketones of widely varying structures. The behavior of bis(α-bromocyclopropyl) ketone (**33**) was different from all others in two respects: (1) it is harder to reduce than other dibromoketones (2) its second bromine is reduced ($E^2_{1/2} = -1.33$ V) markedly with more difficulty than the first one ($E^1_{1/2} = -0.88$ V in MeCN–TEAB). Different results were



obtained under different electrochemical conditions. These results were unexpected since all other dibromoketones gave α-acetoxyketones in high yields.

B. Cathodic Reduction of Cyclopropyl Ketones

Since the cyclopropyl ring mimics the C=C double bond in several processes, most controlled potential electrochemical reductions of cyclopropyl ketones are compared with those of α,β-unsaturated ketones. Polarographic study revealed[64, 67] that the $E_{1/2}$ for the former (Table 8) is in between that of saturated ketones and of α,β-unsaturated ketones. This indicates a possible interaction of the cyclopropyl ring with the carbonyl group. A general mechanism for the electrochemical reduction of cyclopropyl ketones may be outlined as follows. Mandell and coworkers[66] reduced electrochemically two cyclopropyl

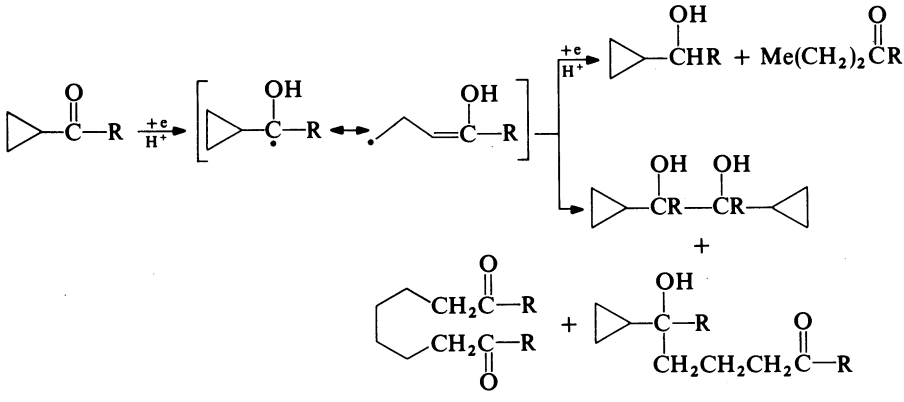


TABLE 8. Reduction potentials of cyclopropyl ketones and related derivatives

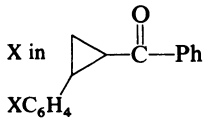
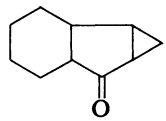
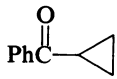
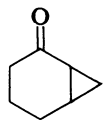
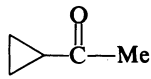
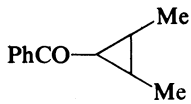
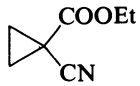
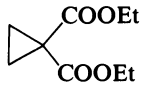
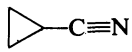
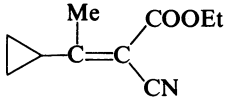
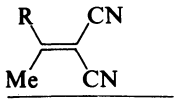
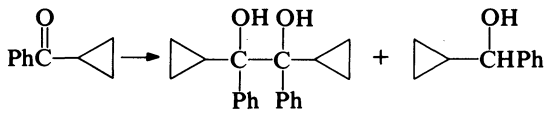
Ketone	$E_{1/2}$ (V vs. SCE)	Medium	Ref.
			
H	−1.000	50% DMF, pH = 2.5	65
H	−1.000	50% EtOH, pH = 3	66
H	−1.82	DMF–TBAF	67
p-F	−0.930, −1.070	50% DMF, pH = 2.5	65
p-Cl	−0.916	50% DMF, pH = 2.5	65
m-Cl	−0.910	50% DMF, pH = 2.5	65
p-Br	−0.912	50% DMF, pH = 2.5	65
p-*i*-Pr	−0.875, −1.000	50% DMF, pH = 2.5	65
p-MeO	−0.870, −0.992, −1.127	50% DMF, pH = 2.5	65
	−2.03	DMF–TBAF	64
	−1.32, −1.40	50% EtOH, pH = 3	66
	−2.07, −2.73	DMF–TBAF	67
	−2.81[a]	DMF–TBAF	67
	−2.87[a]	DMF–TBAF	67
	−2.09	DMF–TBAF	67
	−2.93[a]	DMF–TBAF	67
	−2.98[a]	DMF–TBAF	67
	No wave	DMF–TEAI	68

TABLE 8. *Continued*

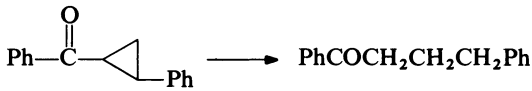
Ketone	$E_{1/2}$	Medium	Ref.
	−1.72	DMF–TEAI	68
			
R = 	−1.69	MeCN–TEAF	69
=  Me (*trans*)	1.71	MeCN–TEAF	69
= 	−1.61	MeCN–TEAF	69

[a] Approximate values.

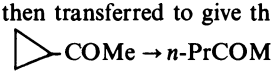
phenyl ketones and obtained products **34** and **35** which demonstrate the one- and two-electron processes, respectively, as well as the formation of ring-opened and ring-retained products. Mairanovskii and coworkers[71] reduced cyclopropyl methyl ketone and



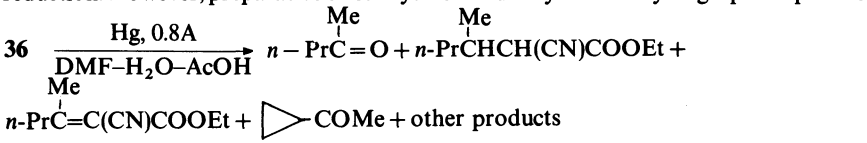
(**34**) (43%) (**35**) (17%)

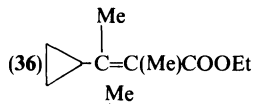


observed a reversible one-electron reduction and subsequent ring-opening of the anion radical. A second electron is then transferred to give the final product.

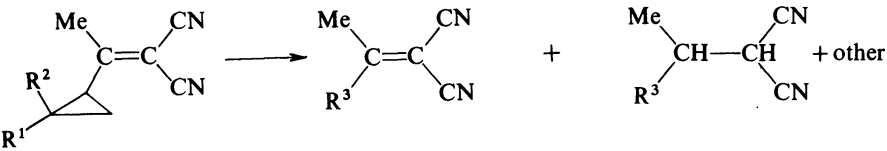


Concerning the interaction of a cylopropyl group with an adjacent activated double bond Baizer and coworkers[68] reported that even when the cyclopropyl ring is adjacent to an electron-withdrawing group it is not electroreducible. The following comparison between **36** and **37** demonstrates that only the activated double bond is involved in the reduction. However, preparative electrolysis of **36** does yield mostly ring-opened products:



	$E_{1/2}$ vs. SCE
(36) 	−1.72
(37) *n*-PrC=C(CN)COOEt	−1.75

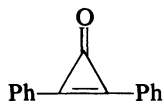
Bellamy and Kerr[69] reduced other olefin-activated cyclopropanes and obtained ring-opening products, also with no dimers:



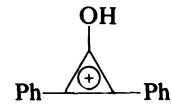
$R^1 = R^2 = H$	R^3 = *n*-Pr (24%)	0–40%
R^1 = H, R^2 = Me (*trans*)	R^3 = *n*-Bu (29%)	3%
$R^1 = R^2$ = Me	$R^3 = Me_2CHCH_2CH_2$ (32%)	8–37%

Jullien and coworkers[70] studied the cyclic voltammograms of variously substituted bicyclo[3.1.0]hexen-3-ones (Table 9) and found that the half-life times ($t_{1/2}$) are generally very short ($\leqslant 10^{-4}$ s) except when the substrates were phenyl-substituted at C(4). In such cases the radical anions are very stable($\geqslant 6$ s) owing to the greater charge delocalization. A similar trend was found in some non-fused cyclopropyl ketones systems studied by House and coworkers[67].

It is noteworthy that there is only one example on the electroreduction of a cyclopropene derivative. A Russian group[72] observed two-electron polarographic waves for the reduction of diphenylcyclopropenone (**38**) in aqueous ethanol. Preparative electrolysis was not carried out and therefore it is not obvious what processes are occurring at each wave. In acid, the same compound exhibits only one polarographic wave. Without



(**38**)



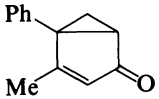
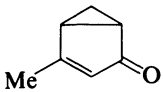
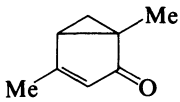
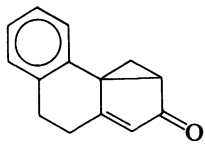
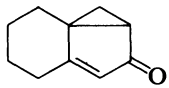
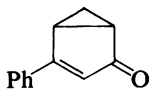
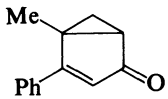
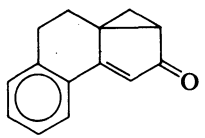
(**39**)

supporting evidence it was suggested that the protonated species (**39**) is reduced to its corresponding radical which then dimerizes.

C. Cathodic Reduction of Cyclopropenyl Cations

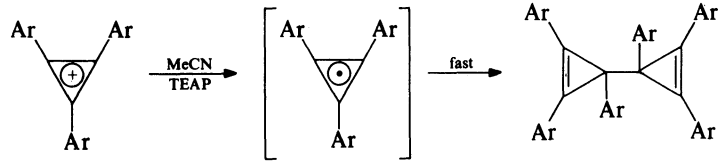
Breslow and coworkers[73] studied extensively the electrochemical reduction of cyclopropenyl cations mainly for the reason of generating a series of cyclopropenyl anions through their corresponding radicals and using electrochemical data for the determination of their basicities.

TABLE 9. Reduction potentials of substituted bicyclo [3.1.0]hexen-3-ones[70]

Substrate	E_p^1 (V vs. SCE)[a]	E_p^2 (V vs. SCE)[b]	$t_{1/2}^c$ (s)
	−2.130[d]		$< 10^{-4}$
	−2.390		$< 10^{-4}$
	−2.470		$< 10^{-4}$
	−2.163		$< 10^{-4}$
	−2.405		$\sim 10^{-4}$
	−1.745[e]	−2.250	6 ± 2
	−1.840[e]	−2.380	> 6 ± 2
	−1.845[e]	−2.380	> 6 ± 2

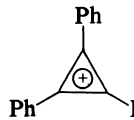
[a] At 300 mV s^{-1} sweep rate.
[b] At 1 V s^{-1} sweep rate.
[c] Half-life time
[d] Each wave corresponds to 1 e except for this one.
[e] This wave is electrochemically irreversible.

DC polarography of three aryl-substituted cyclopropenyl cations (**40**) revealed[73] that a reversible potential could not be obtained due to a rapid dimerization of the intermediate radical formed to give **41**. When fast sweep cyclic voltammetry was employed both cathodic and anodic waves were observed, indicating that the radical can be reoxidized before dimerization.



(40) (41)

A comparison[73, 74] of the reduction potentials of triphenylcyclopropenyl (**40**, Ar = Ph) and triphenylmethyl (**42**) cations indicates that the former is harder to reduce:

		$E^1_{1/2}$(V)	$E^2_{1/2}$(V)
	(**40**, Ar = Ph)	−1.13	−1.56
Ph_3C^+	(**42**)	−0.09	−0.83

This difference in reduction potentials is accounted for by the loss in resonance energy of the stable two π-electron cyclopropenyl cations, whereas the difference in the first reduction process is $\sim$ 1 V ($\sim$ 24 kcal mol^{-1}) it is only 0.7 V in the second reduction process. This reflects a decreased electron repulsion in the larger cyclopropenyl system.

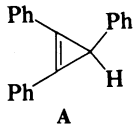
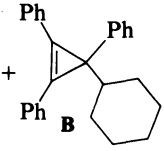
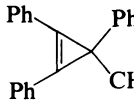
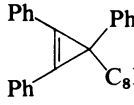
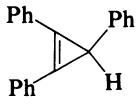
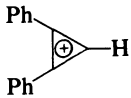
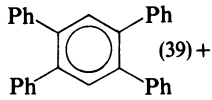
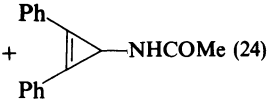
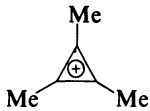
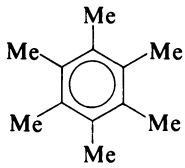
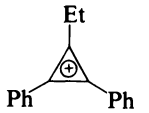
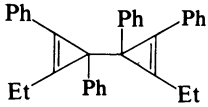
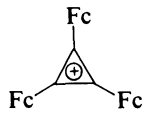
Controlled potential electrolysis at either the first or second reduction wave of **40** (Ar = Ph) afforded[75] only the dimer, a bis(cyclopropenyl) derivative. This is the expected product at the first wave, formed by dimerization of the radical, but at the second wave it corresponds to reaction of the electrogenerated anion with the unreacted cation. Interestingly, the dimer was the only product even in the presence of protic solvents such as AcOH. Later Breslow and Drury[76] succeeded in capturing the anion by protonation with protonated organic bases which are strongly adsorbed at the electrode surface. However, even then, the capture of the anion by the cation was much more effective than the protonation since only 12% of triphenylcyclopropene was formed at potentials beyond $E^2_{1/2}$. It was suggested that the trapping proceeds by an electron transfer followed by coupling of the resulting radicals. Evidence which supports the mechanism of anion–cation coupling has been reported[77].

Shono and coworkers[78] studied the electrochemical formation of triphenylcyclopropenyl radical and its chemical behavior in the presence of hydrogen donors and olefins (Table 10). Wasielevsky and Breslow[79] studied the reduction of various cyclopropenyl cations by second harmonic AC voltammetry (Table 11). They detected adsorption effects for some of the cations at the Pt but not at the Au electrode. The electrochemical data were used in thermodynamic sequences to evaluate the basicity of various cycloproenyl anions as well as the C–O bond dissociation energy of cyclopropenols.

D. Cyclopropyl Ring-opening by Anodic Oxidation

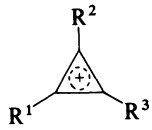
Ring-opened products were obtained in the anodic oxidation of various cyclopropyl derivatives. Shono and Matsumura[81] studied the oxidation of arylcyclopropanes (Table 12) and their products suggest that the reaction is initiated by the oxidation of the aromatic

TABLE 10. Preparative electrochemical reduction of cyclopropenyl cations

Cation	Added substrate	Products (%)	Ref.
41 (Ar = Ph)	—	Dimer (61)	78[a]
	—	Dimer (90)[b]	75
		 (7.5) +  (2.4) + dimer (26) **A** **B** **C**	78[a]
	$CHCl_3$	**A** (6.9) + **C** (23.8)	78[a]
	$PhCH=CH_2$	 (7.3) + $Ph(CH_2)_4Ph$(?) + dimer (28)	78[a]
	1-Octene	 (6.7) + dimer (28)	78[a]
	Guanidinium perchlorate	 (12) + dimer (major)	76
	—	 (39) +  (24)	78[a]
	—		75[c]
	—	 (quantitative)[d]	77
	—	Dimer	80

[a] Electrolyses were carried out in MeCN–$LiClO_4$, at graphite employing constant current of 0.3 A.
[b] In MeCN or MeCN–AcOH (1:1) at −2.3 V, at mercury cathode. No triphenylcyclopropene was detected.
[c] CPE at the first reduction wave.
[d] CPE *at* 0.84 *V. Beyond* E_2 = 1.78 V the yield of the dimer was reduced to 73%.

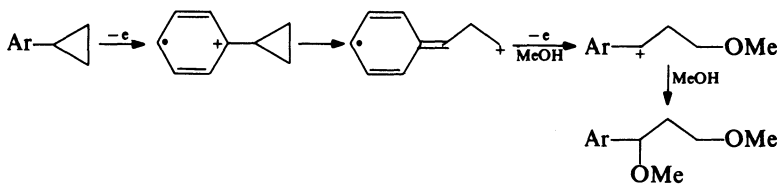
TABLE 11. Reduction potentials of cyclopropenyl cation derivatives[a]



R^1	R^2	R^3	Anion	Medium	Cathode	$E^1_{1/2}$	$E^2_{1/2}$	Ref.
Ph	Ph	Ph	ClO_4^-	DMSO–TBAP	Pt	−0.85	−1.73	75
Ph	Ph	Ph	BF_4^-	HMPA–TBAP	Pt	−1.12	−1.56	74
Ph	Ph	Ph	ClO_4^-	MeCN–TEAP	Pt	−0.75		73
Me	Me	Me	ClO_4^-	DMSO–TBAP	Pt	−1.32	−2.22	75
n-Pr	*n*-Pr	*n*-Pr	BF_4^-	DMSO–TBAF	Pt	−1.36	−2.30	75
t-Bu	*t*-Bu	t-*Bu*	ClO_4^-	DMSO–TBAP	Pt	−1.53	−2.12	75
Ph	Ph	An[b]	ClO_4^-	DMSO–TBAP	Pt	−0.86		73
An	An	An[b]	ClO_4^-	DMSO–TBAP	Pt	−1.11		73
H	H	H	BF_4^-	MeCN–TBAP	Au	−0.62	−1.78	79
				MeCN–TBAP	Pt	−0.23	−1.95	79
Me	Me	Me	BF_4^-	MeCN–TBAP	Au	−1.74	−2.28	79
				MeCN–TBAP	Pt	−1.16	−2.20	79
t-Bu	*t*-Bu	*t*-Bu	BF_4^-	MeCN–TBAP	Au	−1.65	−2.25	79
				MeCN–TBAP	Pt	−1.69	−2.25	79
n-Pr	*n*-Pr	H	BF_4^-	MeCN–TBAP	Au	−1.16	−1.90	79
				MeCN–TBAP	Pt	−1.17	−1.91	79
Ph	Ph	Ph	ClO_4^-	MeCN–TBAP	Au	−0.72	−1.66	79
				MeCN–TBAP	Pt	−0.72	−1.60	79
Ph	Ph	Et	ClO_4^-	MeCN	Hg	−0.84	−1.98	77
Fc	Fc	Fc[c]	BF_4^-	MeCN–TBAPF_6	Hg	−1.33	−2.05	80

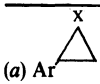
[a] $E_{1/2}$ for the waves was taken at 85% of the peak height observed in cyclic voltammetry, at scan rates up to 45 V s^{-1} (Refs 73–75). Potentials in Ref. 79 were measured by second harmonic AC polarography.
[b] An = *p*-$MeOC_6H_4$,
[c] Fc = Ferrocenyl.

nucleus to a cation radical. The latter interacts conjugatedly with the cyclopropyl ring followed by 1,3-addition of nucleophiles with ring-opening. They discuss several plausible mechanisms of which a preference was given to the following one, demonstrated for

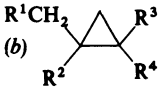


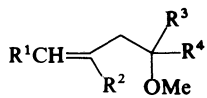
Ar = Ph. It is noteworthy that the oxidation of arylcyclopropanes by metallic acetates also yielded ring-opened products but the mechanism suggested involved an electrophilic attack of the oxidizing reagent on the cyclopropyl ring[82].

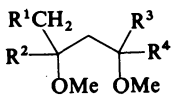
TABLE 12. Anodic oxidation of aryl and alkyl substituted cyclopropanes

(*a*) 

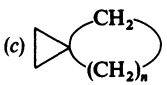
Ar	X	$E_{1/2}$(V vs. SCE)[a]	Products (yield, %)[b]	Ref.
Ph	H	1.87	PhCH(OMe)CH_2CH_2OMe (74)[c]	81
Ph	Me	1.71	PhCH(OMe)CH_2CH(OMe)Me (71)	81
Ph	Ph	1.44	PhCH(OMe)CH_2CH(OMe)Ph (66)[d]	81
Ph	OMe	1.46	PhCH(OMe)CH_2CH$(OMe)_2$ (64)[e]	81
p-MeC_6H_4	H	1.59	*p*-MeC_6H_4CH(OMe)CH_2CH_2OMe (62)	81
2,4,6-$Me_3C_6H_2$	H	1.67	2,4,6-$Me_3C_6H_2$CH(OMe)CH_2CH_2OMe (60)	81
p-$MeOC_6H_4$	H	1.35	—[f]	81
p-ClC_6H_4	H	1.97	—[f]	81
2,4,6-$Me_3C_6H_2$	Me	1.61	—[f]	81
2,4,6-$Me_3C_6H_2$	OMe	1.48	—[f]	81

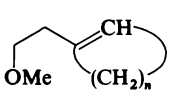
(*b*) 

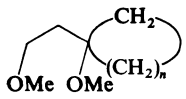




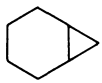
$R^1 = H, R^2 = R^3 = R^4 = Me$	47	24	90
$R^1 = R^4 = H, R^2 = R^3 = Me$	11	10	90
$R^1 = Me, R^2 = Et, R^3 = R^4 = H$	—[g]	12	90

(*c*) 

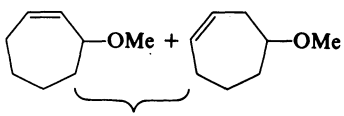




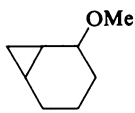
$n = 4$	1	5	90
$n = 2$	—[g]	26	90
$n = 1$	—[h]	—[h]	90



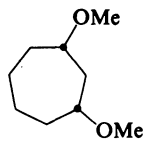
1.3



(23–48) 83



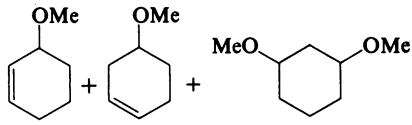
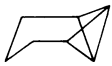
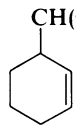
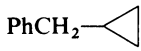
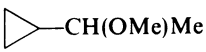
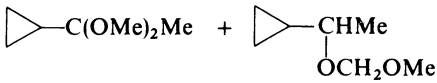
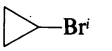
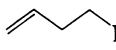
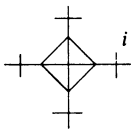
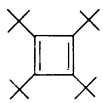
(8–35)



cis: 11–13
trans: ~ 10

+ $CH_2 = CH(CH_2)_4CH(OMe)_2$ (~ 20)

TABLE 12. *Continued*

(a) ArΔ^{X} Ar	X	$E_{1/2}$ (V vs. SCE)[a]	Products (yield, %)[b]	Ref.
		1.3	$CH_2=CH(CH_2)_3CH(OMe)_2$ (~ 18)	83
			 (23) (24) (*cis.* 19.5; *trans:* ~ 15)	
			 (~ 60) + 4 other products	84
			 (25)	81
			 (~ 8 total)	85
				44
		0.5 (at-70° C)		86

[a] Oxidation potentials were determined in MeOH-$LiClO_4$ at Pt anode.
[b] Preparative electrolysis was carried out in MeOH–TEAOTs at room temperature on carbon anode and with supplied voltage of 18–40 V,
[c] Controlled potential oxidation at 1.70 V vs. SCE gave the product in ~ 97% yield.
[d] A mixture of two isomers (1:1).
[e] The reaction was carried out at −30 to −40 °C.
[f] No preparative electrolysis was carried out.
[g] The compound was not isolated because of its further oxidation.
[h] The compound was anodically stable under the conditions studied.
[i] In MeCN.

The presence of an aromatic substituent is not a necessary condition for cyclopropyl ring-opening. Such a process was found to take place also in the anodic oxidation of alkyl substituted cyclopropanes (cf. entries (*b*) and (*c*) in Table 12). It is noteworthy that the structures or distributions of the products obtained from the anodic oxidation of

bicyclo[3.1.0]hexane (entry (*c*) in Table 12) were completely different from those observed in the acid solvolyses, or in the metallic oxidations or radical reactions of either one of the bicyclic hydrocarbons. Thus it was concluded that the electrochemical process was initiated by the direct oxidation and cleavage of the internal C–C bond of the cyclopropane ring, exclusively.

The anodic oxidation of polyalkyl substituted cyclopropanes and spiro[2.*n*]alkanes gave mono- and dimethoxy products which resulted from the cleavage of the most highly substituted C–C bond, in contrast to the results obtained by acid-catalyzed methanolysis of alkyl-substituted cyclopropane by the same authors. Those results suggest that a direct σ-electron transfer from the most strained σ bond of cyclopropane to the anode may be the initiation step.

Ring-opened products were observed in various cyclopropyl substituted systems. The anodic oxidations of gem-dichlorocyclopropyl derivatives[87] as well as of cyclopropanes substituted with a thiophenoxy group[88] (Table 13) were investigated. The reaction probably proceeds via the radical cations of these substrates which undergo C–C bond cleavage with ring-opening and subsequent solvolysis, deprotonation and oxidation. Interestingly, unsaturated acetals or esters were formed from the cation radicals of gem-dihalocyclopropyl derivatives. Contrary to Klehr and Schäfer's results[87] different types of ring-opening take place in the anodic oxidation of 1-methyl-2-(phenylthio)cyclopropanes

TABLE 13. Ring-opened products from the anodic oxidation of alkoxy- and thiophenoxy cyclopropyl derivatives in MeOH

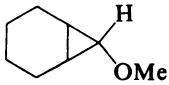
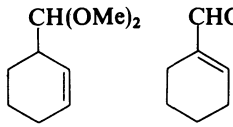
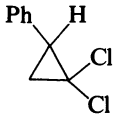
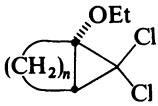
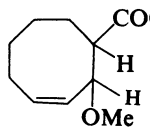
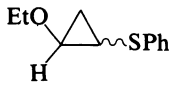
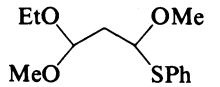
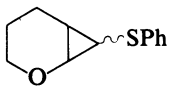
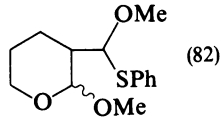
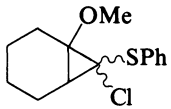
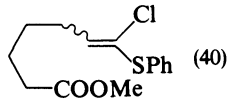
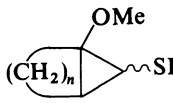
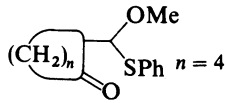
Substrate	E_p(V vs. SCE)	Products (yield, %)[a]	Ref.
	1.64		87
	1.83	$PhCH(OMe)CH_2COOMe$ (57) + $PhCH=CHCOOMe$ (37, *trans*)	87
 $n = 4$	1.65	$Cl_2C=CH(CH_2)_4COOMe$ (86)	87
$n = 5$	1.65	$Cl_2C=CH(CH_2)_5COOMe$ (77) $Cl_2C=CH(CH_2)_5COOEt$ (11) $MeCOO(CH_2)_5CH(Cl)COOMe$ (1)	87
$n = 6$	1.65	$Cl_2C=CH(CH_2)_6COOMe$ (21) $Cl_2C(OMe)CH(OMe)(CH_2)_6COOMe$ (9) 	87

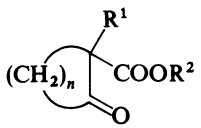
TABLE 13. *Continued*

Substrate	E_p(V vs. SCE)	Products (yield, %)[a]	Ref.
	3[c, d]	 (93)[b]	88
	3[c]	 (82)	88
	3[c]	 (40)	88
 $n = 4$	3[c]	 $n = 4$ (98)	88
$n = 5$	4[c]	$n = 5$ (79)[e]	88
$n = 10$	5[c]	$n = 10$ (78)	88

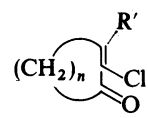
[a] Based on reacted starting material or isolated products.
[b] When electrolyzed without K_2CO_3 the yield of the product decreased to 72% (+ ~ 20% of PhSSPh).
[c] Constant applied voltage.
[d] The anodic potential is 0.9 V vs. SCE.
[e] The yield increases to 93% in the presence of excess of K_2CO_3.

in methanol–Et_4NOTs and in the presence of K_2CO_3, as shown in Table 13[88]. It was found that the nature of substituents on the cyclopropyl ring is important for determining the product selectivity.

Torii and coworkers[89] developed a convenient method for the introduction of an alkoxycarbonyl group at the α-positions of cycloalkanones. It involves a novel anodic cleavage at one of the external C–C bonds of the cyclopropane in the presence of Fe^{3+} ions, leading to the formation of cyclic β-keto esters (**43**) in 39–79% yield (Table 14). The reaction temperature has a profound effect on the yield of **43** since at the higher temperature range the formation of **44** was favored.



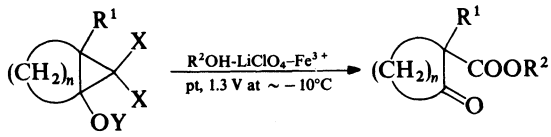
(**43**) (R^1 = H, Me)



(**44**) (R^1 = H)

The electrochemical oxidation of strained and non-strained aliphatic cyclopropyl derivatives was examined in MeCN. The results are summarized in Table 15. Clearly, the strained hydrocarbons are more readily oxidized compared with the non-strained systems.

TABLE 14. Anodic generation of β-keto esters from alkoxy- and halo-substituted bicyclo[*n*.1.0] derivatives[89]



R^1	Y	X	*n*	R^1	R^2	Yield (%)
H	$SiMe_3$	H	4	H	Me	72
H	$SiMe_3$	Br	4	H	Et	77
H	$SiMe_3$	Cl	5	H	Me	73
			5	H	Et	79
Me	$SiMe_3$	Cl	10	H	Me	39
H	H	Cl	10	H	Et	48
H	Et	Cl	4	Me	Me	56
			4	Me	Et	61

TABLE 15. Anodic potentials of strained and non-strained cyclopropyl hydrocarbon derivatives

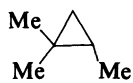
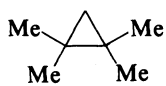
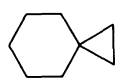
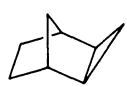
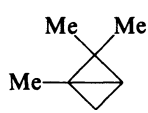
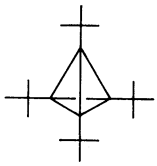
Substrate	*E*(V vs. SCE)	Ref.
	> 2.5[a]	90
	2.30[a]	90
	2.05[a]	90
	2.38[a]	90
	2.40[a]	90
	0.91[b]	84
	1.23[b]	84

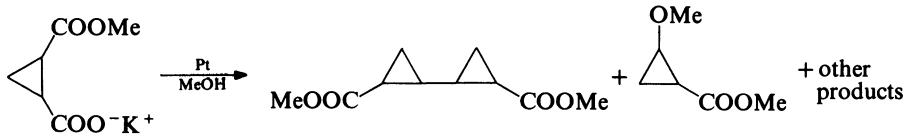
TABLE 15. *Continued*

Substrate	E(V vs. SCE)	Ref.
	1.50[b]	84
	1.54[b]	84
	1.54[b]	84
	1.62[b]	84
	1.91[b]	84
	2.12[b]	84
	0.5[c]	86

[a] In MeCN–TEAF. Reported values correspond to peak potentials.
[b] In MeCN–$LiClO_4$ at 100 mV s^{-1}. Reported values correspond to $E_{1/2}$.
[c] In MeCN–TBAF at −70 °C at glassy carbon. Sweep rate 50 mV s^{-1}.

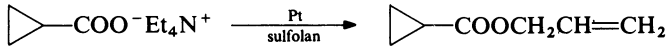
E. Anodic Oxidation of Cyclopropyl Carboxylate Derivatives

Back in 1929 Fichter and Spiegelberg[91] electrolyzed sodium methyl *cis*-cyclopropane-1,2-dicarboxylate in MeOH and in H_2O. In each case they obtained a low yield of an ester corresponding to the Kolbé-coupled product. Their suggested structural assignment for the ester was apparently wrong since others[92,93] reinvestigated the reaction and found the ester to be dimethyl biscyclopropyl-2,2′-dicarboxylate (**45**), among other products.



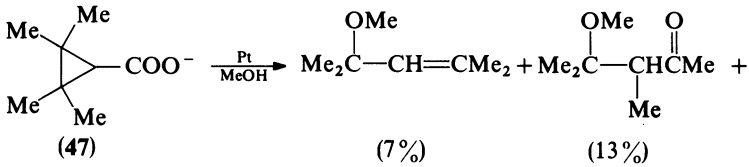
(**45**) (25%)

However, when they oxidized tetraethylammonium cyclopropyl carboxylate (**46**) no Kolbé dimer was formed but an allylic ester was formed instead. In contrast to this result,

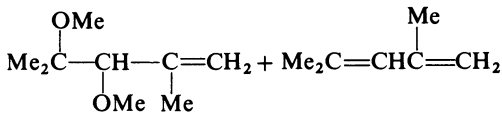


(**46**)

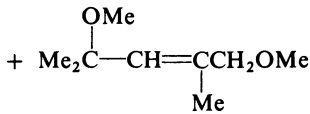
Fichter previously reported that electrolysis of cyclopropanecarboxylic acid yields no products with retained ring[94]. This was found to be the case in the oxidation of alkyl-substituted cyclopropanecarboxylic acids. Thus the anodic oxidation[95] of 2,2,3,3-tetramethylcyclopropane-1-carboxylate (**47**) yielded no Kolbé dimer but six other main



(**47**) (7%) (13%)

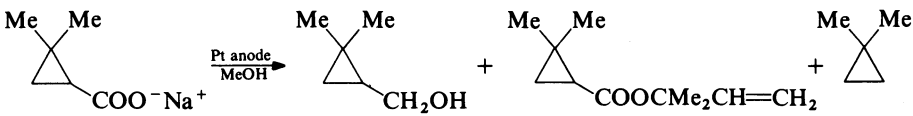


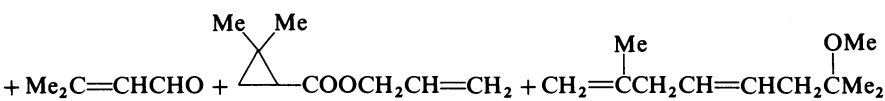
(6%) (3.5%)

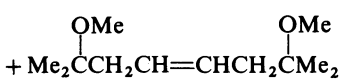


(2 geometrical isomers, 5% + 7%)

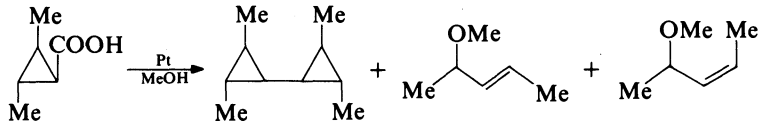
products. Binns and coworkers[96] also did not find a Kolbé dimer from the oxidation of 2,2-dimethylcyclopropane-1-carboxylate but identified ten other products, some with retained



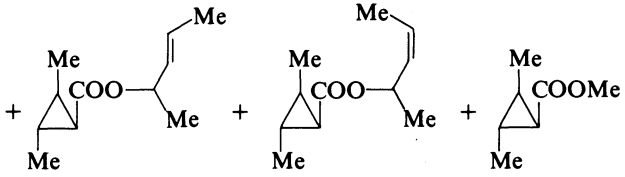




ring: To add to the complexity, the major product in the electrolysis[97] of *trans*-2,3-dimethylcyclopropanecarboxylic acid (**48**) is the Kolbé dimer, formed by coupling two cyclopropyl radicals, together with the products listed below and eight other unidentified

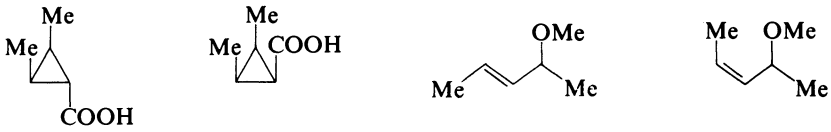


(**48**) (41.4%) (16.1%) (11.6%)



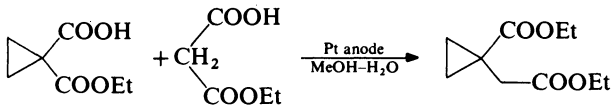
(9.1%) (6.3%) (3.6%)

products (totaling 11.9%). Other isomers (**49** and **50**) were oxidized too, and each yielded a mixture of two isomers of the Kolbé dimer as the major product. In addition either **49** or **50** yielded **51** and trace amounts of **52**.



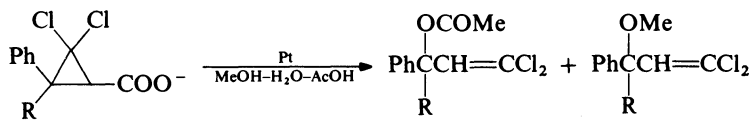
(**49**) (**50**) (**51**) (**52**)

Denis and coworkers[93] showed that in a mixed Kolbé, a coupled product **53** could be obtained in the following way:



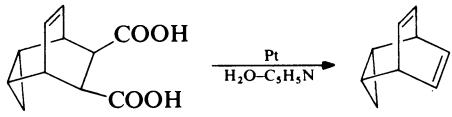
(**53**) (18%)

A Japanese group[98] showed that ring-opening (with subsequent solvolysis rather than coupling) occurs in the anodic oxidation of gem-dichlorocyclopropylcarboxylate derivatives (**54**). Small amounts of PhCHO, PhCOOMe, PhCOMe, $PhCH_2OH$ and other products, were also formed.

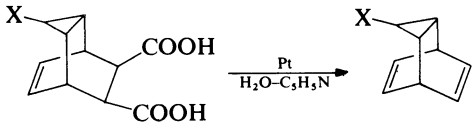


(**54**)

It should be pointed out that when the carboxylic group is not directly attached to the cyclopropyl ring the latter is stable and no ring-opening takes place during the course of the anodic decarboxylation. Two examples are shown below:



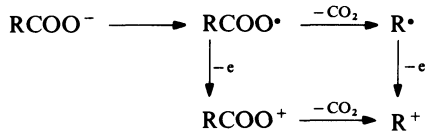
(Ref. 99)



(Ref. 39)

X = H, CN

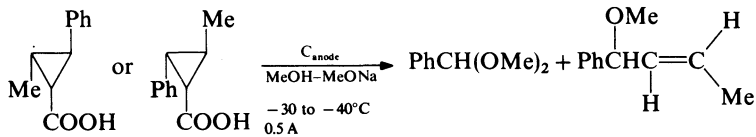
The preceding examples revealed that the anodic decarboxylation of cyclopropylcarboxylic acid derivatives in methanol is a diverse process and may lead to Kolbé dimers, ring-opening and ring-retained products. A postulated mechanism in which all the cyclopropyl methyl ether products are formed by combination of cyclopropyl and methoxy radicals is excluded by the observation that anodic oxidation of 1-methylcyclopropane-2-acetic acid on carbon electrodes yields methyl ethers of which 99.4% are formed by carbenium ion rearrangements[100]. When the corresponding radical is generated chemically no rearrangement products are observed[101]. There are at least two conceivable routes for the generation of a cationic intermediate in the anodic decarboxylation. The essential



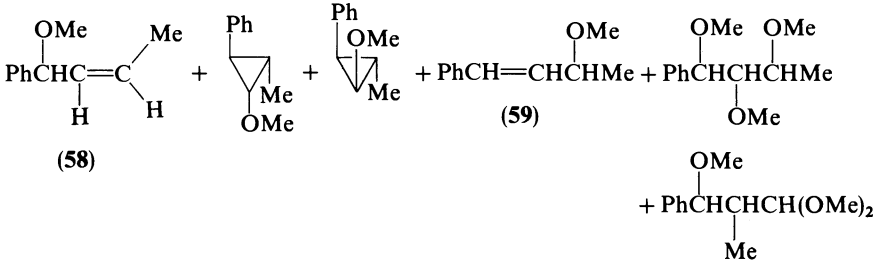
(route A)

(route B)

difference between them is that route A yields both radicals and carbocations while route B yields both acyloxonium ions and carbocations. When R is a cyclopropyl ring it is generally accepted that a cyclopropyl radical does not retain its stereoconfiguration and does not yield ring-opened products at low reaction temperature[102]. However, a cyclopropyl cation opens to give allylic products but nonstereospecifically[103]. On the other hand the elimination of CO_2 from the intermediate cyclopropyloxonium ion (route B) must result in a concerted ring-opening of the cyclopropyl ring yielding stereospecific allylic products. By using this reasoning Shono and coworkers[104] found evidence for route B. They investigated compounds **55** and **56** at the carbon anode in MeOH–MeO^-Na^+ and obtained ten products of which they identified eight. Compound **55** did not form product **57**, and **56** did not form **58** and **59**. According to the authors these results indicate that the



(55) (56) (57)



(58) (59)

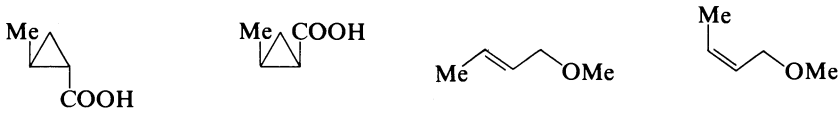
allylic products **57–59** were formed through a stereospecific ring-opening, suggesting the generation of an intermediate acyloxonium ion in the anodic decarboxylation reaction.

Shono and coworkers[104] also investigated the anodic decarboxylation of **60** and **61** and obtained a similar result which supports the formation of acyloxonium ion which

(60) (61)

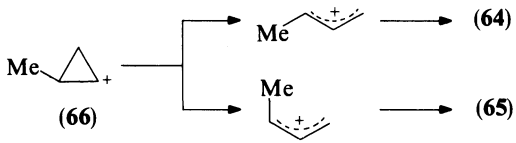
subsequently ring-opens. It is noteworthy that in the oxidative decarboxylation by $Pb(OAc)_4$ the acyloxonium ion was not involved as an intermediate, but a cyclopropyl radical was generated and oxidized to the cationic species by the metal ion[105].

Rodewald and Lewis[97] oxidized *trans*- and *cis*-2-methylcyclopropane-1-carboxylic acids (**62** and **63**) both on Pt and C anodes and from each they obtained the mixture of the isomers **64** and **65**, in about 4:1 ratio. Based on these results they concluded that a



(62) (63) (64) (65)

common intermediate, the 2-methylcyclopropyl cation (**66**), is traversed in each case, excluding a mechanism in which ring-opening takes place during (or before) the decarboxylation of the RCO_2^+ ion.



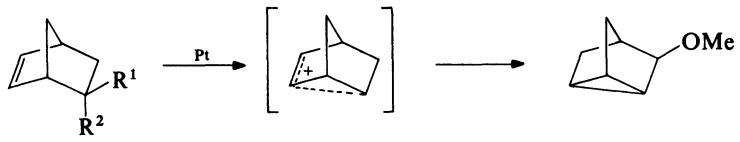
(66)

IV. A CYCLOPROPYL RING AS AN INTERMEDIATE OR A BRIDGED-ION IN ELECTROCHEMICAL PROCESSES

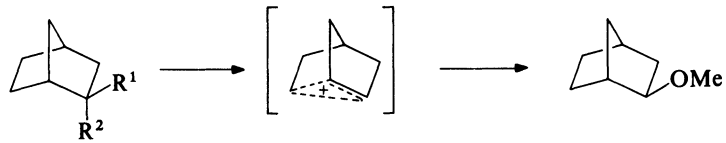
It is well established that the Kolbé synthesis of hydrocarbons from carboxylate ions $\left(RCO_2^- \xrightarrow[-CO_2]{-e} \tfrac{1}{2}RR\right)$ could be extended by another stage of electron transfer to generate

carbocations. The anodic synthesis of such ionic species depends on various factors such as the anode material and the applied potential and is especially favorable with those structures which give rise to relatively stable carbocations.

Corey and coworkers[106] suggested that cyclic cationic intermediates are involved in the formation of 3-methoxynorticyclene (**68**) from either *endo-* or *exo*-5-norbornene-2-carboxylic acid (**67**), and for the formation of *exo*-2-methoxynorbornane (**70**) as the only volatile product from the electrolysis in MeOH (at Pt anode) of either *exo-* or *endo*-norbornane-2-carboxylic acid (**69**). These results are consistent with the suggested formation of the same bridged ions in the solvolysis reaction[107].



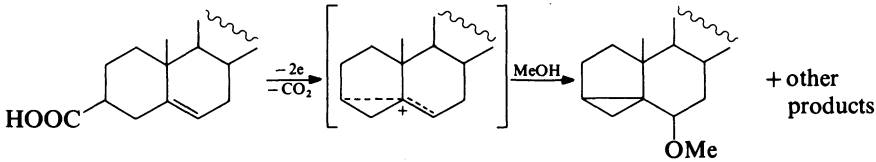
(**67**) (**68**) (56%)



(**69**) (**70**)

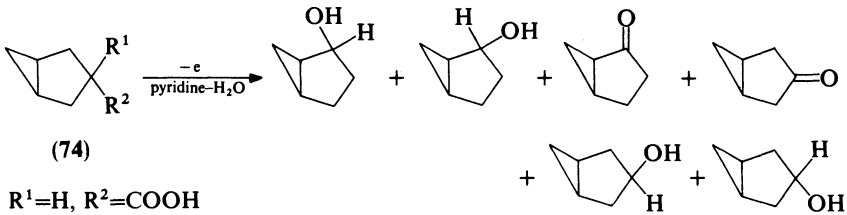
R^1=H, R^2=COOH or R^1=COOH, R^2=H

In the electrolysis[106] of the Δ^5-cholestene-3β-carboxylic acid (**71**) three products were identified. The product containing a cyclopropyl ring (**73**), is possibly formed via the bridged cationic intermediate (**72**).



(**71**) (**72**) (**73**)

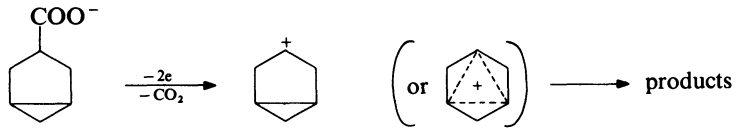
The electrolytic decarboxylations of either *cis-* or *trans*-bicyclo[3.1.0]hexane-3-carboxylic acids (**74**), gave[108] the same products although in different ratios. The



(**74**)

R^1=H, R^2=COOH
R^1=COOH, R^2=H

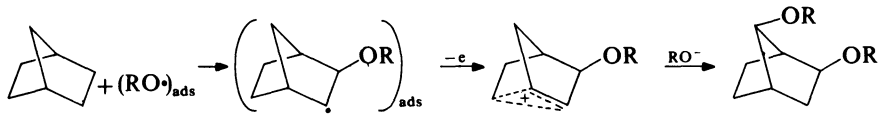
formation of the rearranged alcohols was ascribed to the capture of a cationic intermediate by the solvent and raised the question of the intermediacy of trishomocyclopropenyl cations (**75**). The results of the electrolysis of 6-deuterio-*cis*-bicyclo[3.1.0]hexane-3-



(**75**)

carboxylic acid showed that **75** is not an intermediate in the formation of the corresponding 2-alcohols since no deuterium scrambling was observed.

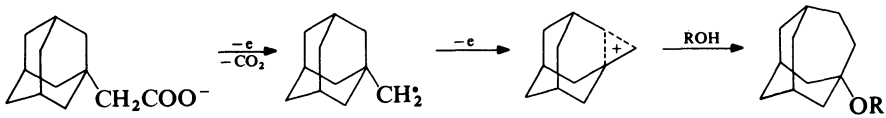
Homolytic alkoxylation of olefins by anodic oxidation of alcohols[109] gave products of which some were suggested to be formed through the intermediacy of the bridged positive ions (**76**):



(ads = adsorbed onto the electrode sueface)

(**76**)

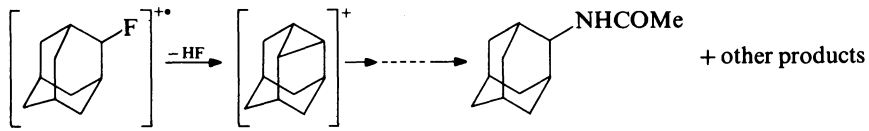
In the electrolysis[110] of 1-(adamantyl)acetic acid in alcohols the only products isolated were the 3-homoadamantyl ethers, possibly formed via the cyclopropenyl cation intermediates (**77**). The same result in methanol was published by a Russian group[111].



(**77**)

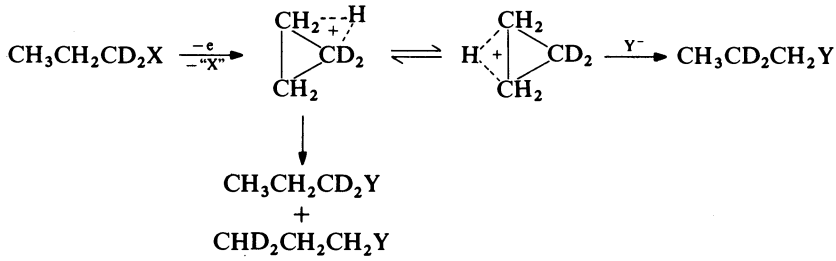
R = Me, 72%
R = Et, 65%

Vincent and coworkers[112] oxidized 2-fluoroadamantane in MeCN and obtained a product derived from substitution of the fluorine by an acetamido group. They explained this result by suggesting an elimination of HF from the corresponding cation radical (**78**),

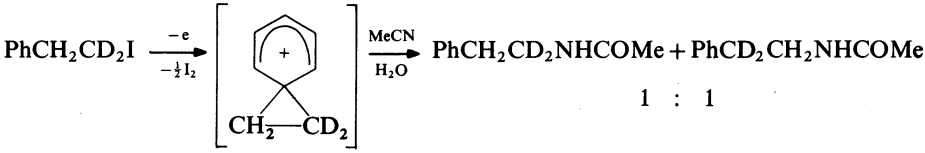


(**78**)

gaving a cyclopropyl cation intermediate. Cyclic carbenium ions were also postulated for explaining some of the results obtained in the anodic oxidation of primary alkyl iodides[113], in analogy to the solvolysis of labelled primary halides[114]. Laurent and Tardivel[115] have presented clear evidence for a Wagner–Meerwein rearrangement during

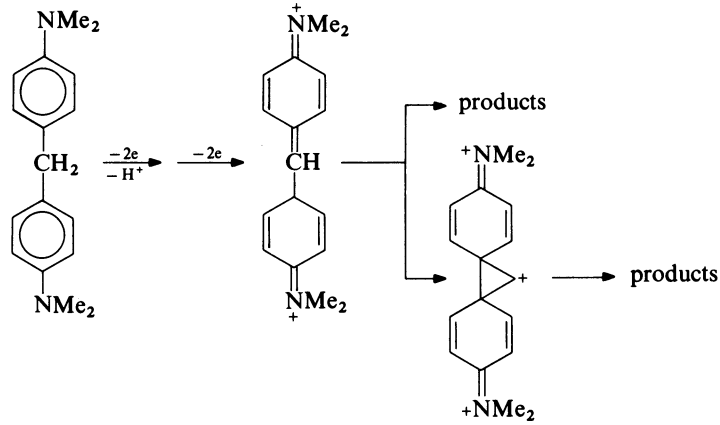


the oxidation of β-phenethyl iodide-α,α-d_2, in which they postulated the involvement of the phenonium ion (**79**):



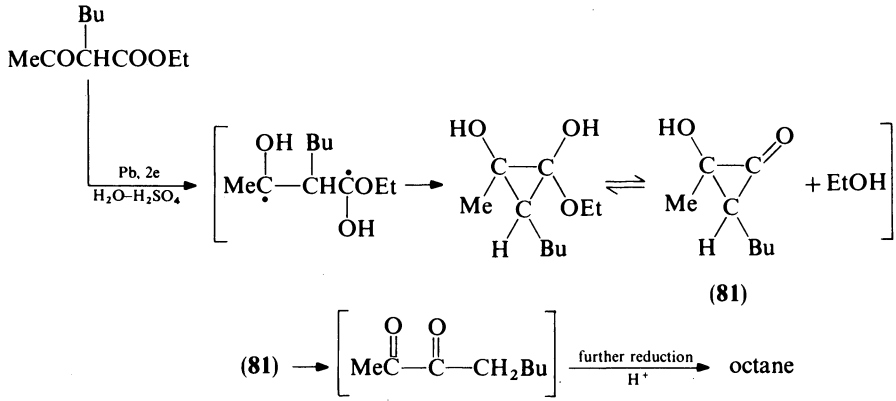
(**79**)

Participation of two phenyl rings in the formation of a cyclopropane intermediate (**80**) was proposed for the anodic oxidation of tri- and diarylmethanes as shown below.



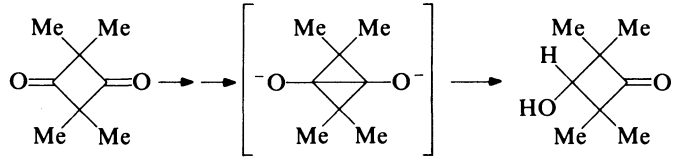
(**80**)

Intermediate formation of a cyclopropyl ring has also been suggested in electrochemical reductions although to a lesser extent. 2-Alkyl-substituted acetoacetic esters undergo the Tafel rearrangement[116] upon reduction at a lead cathode in an acidic medium with complete reduction of the functional groups[116,117]. Analysis[118] of the reduction products of ethyl α-butylacetoacetate, indicates that the Tafel rearrangement may proceed through a cyclopropane and cyclopropanone intermediates. Attempts to trap **81** with anthracene as a Diels–Alder adduct were unsuccessful, suggesting that the concentration of the hydroxycyclopropanone is low because of its rapid rearrangement to 2,3-octanedione.



(81)

The cathodic reduction of 2,2,4,4-tetramethylcyclobutanedione leads to the formation of the l-hydroxy-3-cyclobutanone derivative. It was proposed that this product is formed via the intermediacy of a bicyclobutane derivative (**82**).



(82)

Tafel-type rearrangement[116] was found to occur in the cathodic reduction of β-diketones. This is in agreement with the involvement of cyclopropanediol intermediates in this reduction[32].

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CHAPTER **16**

Biochemistry of the cyclopropyl group

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I. INTRODUCTION

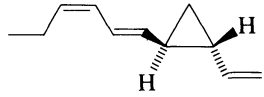
The cyclopropyl group is found as a structural element in a wide range of naturally occurring compounds, in plants and in microorganisms, both fungal and bacterial. In many cases the cyclopropyl functionality is a stable structural entity in secondary metabolites, while in others a cyclopropanoid intermediate is generated transiently as a connecting element between a substrate and a final product both in primary and secondary metabolism.

Representative cyclopropanoid compounds in nature can be classified according to the structural framework of the molecule and/or the substitution on the cyclopropyl moiety and these initial categorizations are taken up below.

A. Representative Structures

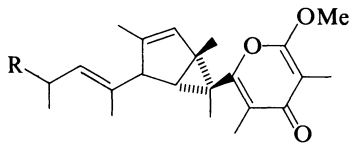
1. Polyacetates

Dictyopterene B (**1**) is one of the polyacetate-derived cyclopropane-containing natural products and is isolated from the essential oil of brown algae *Dictyopteris plagiogramma* and *D. australis*[1]. This tri-olefinic cyclopropane is a sex pheromone released by the female plants to attract male gametes. This unusual C_{11} hydrocarbon along with other *Dicyopteris* constituents has a characteristic odor associated with ocean beaches. A second



(1)

example is represented by crispatene (2) and erispatene (3) from the sacoglossan *Tridochia crispata*, a photosynthetic ophistobranch mollusc[2].

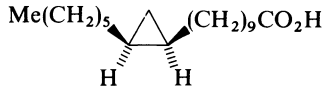


R : $MeCH_2C(=O)$— crispatene (2)

R : H erispatene (3)

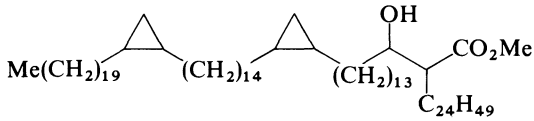
2. Fatty acids

Cyclopropane-containing fatty acids are well known compounds of bacterial membranes. Lactobacillic acid (4) has been isolated from *Lactobacillus arabinosus*[3–5], *Brucella abortus* and *B. melitensis*[6,7]. Congeneric cyclopropyl fatty acids of C_{17}, C_{19}, and C_{21} constitution have been seen in many Gram-negative and Gram-positive bacteria[8]. From



(4)

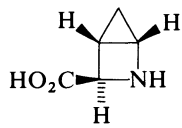
the human strain of tubercle bacilli, *Mycobacterium tuberculosis var. hominis*, methyl hominomycolate-I (5), a homologue of mycolic acid-I, has been found as a major component of the mycobacterial cell envelope[9,10].



(5)

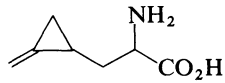
3. Amino acids

In the amino acid family are a number of interesting cyclopropyl compounds including the bicyclic methanoproline (6), produced by *S. zamoyceticus* SF-1836[11] with antibacterial activity against *Xanthomonas* and *B. subtilis* strains. The compound is apparently a proline



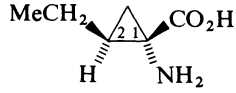
(6)

analog since this activity is reversible by proline[12]. Hypoglycine A (**7**), a methylidene cyclopropanoid amino acid, is found in the unripe fruit of the akee fruit, *Blighia sapida Kon.* (Sapindaceae)[13–15] and is the causative agent in Jamaican vomiting sickness with



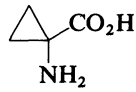
(**7**)

associated hypoglycemia[15]. The mode of action of this agent will be discussed in Section IV. Coronamic acid (**8**), the 1*S*,2*S* isomer, is the amido component of coronatine, a toxin



(**8**)

produced by *Pseudomonas soronafacience var. atropurpurea* which induces chlorosis on leaves of rye grass and lyses potato cells at concentrations of 10^{-7} M[16–18]. The parent 1-aminocyclopropane-1-carboxylic acid (**9**) is also known (ACPC) and is a common constituent in apple, pear, grapefruit and many other plant tissues[19,20]. The metabolism of

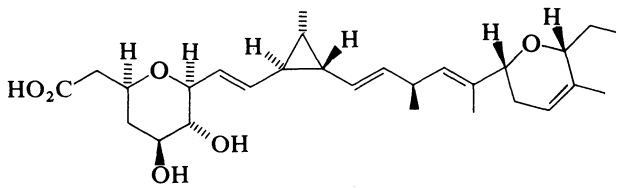


(**9**)

ACPC to ethylene, a fruit-ripening and growth-regulating plant hormone[21] will be analyzed later in this chapter.

4. Polyether antibiotics

Ambruticin (**10**) is an antifungal antibiotic present in the fermentation medium of *Polyangium cellulosum var. fulvum*[22,23]. It is highly active against systemic pathogenic fungi such as *Histoplasma capsulatum* and *Coccidioides immitis.*

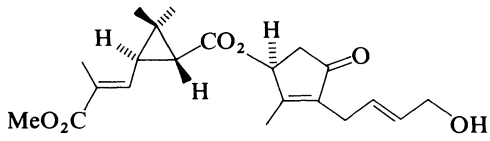


(**10**)

5. Terpenoids

Cyclopropane-containing terpenoids make up a large and varied class of naturally occurring cyclopropanoids. Among them is pyrethrin (**11**), the rethrolone ester of

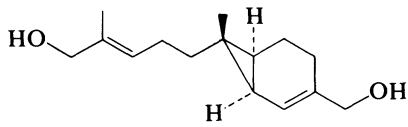
pyrethric acid. It is present in the flower heads of *Chrysanthemum cinerariaefolium*[24] and has a defense function in these plants. This cyclopropane-containing metabolite is very effective as an antifeedant for herbivores and also has a broad spectrum as an insect repellant. The mechanism of insecticidal action has been attributed to blockade of the



(11)

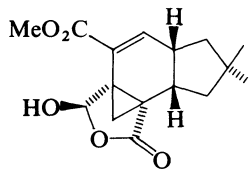
sodium channel in target cell membranes[25,26] and consequent blockade of ion transport. An enormous effort has gone into the successful development of synthetic pyrethroids as commercial insecticides following these observations but further details of pyrethroid pharmacological mechanism are unknown.

Sirenin (**12**) is a powerful sperm attractant produced by the female gametes of the water mold *Allomyces sabuiscula* and A. *javanicus*[27,28]. It is one of the chemostactic and chemotropic agents that serve as the prelude for fertilization. This compound is synthesized prior to the organism's emergence from the gametangia, and is released into the ambient liquid environment. Sirenin (**12**) is biologically active at concentrations of 10^{-10} M. A compound, sesquicarene, possessing the parent skeleton has been isolated from essential oil of *Schysandra chreum*[29].



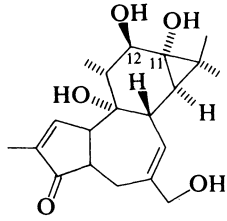
(12)

Marasmic acid (**13**) was isolated from the basidiomycete *Marasmium conigenus* (mold). This compound possesses potent antibacterial activity against *Staphylococcus aureus* and *E. coli*[30] although no mechanism of action has been established.



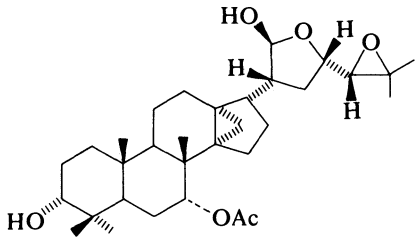
(13)

Phorbol (**14**) was isolated from the oil of *Croton tiglium* (Euphorbiaceae) seeds[31–34]. The presence of a system containing both the cyclopropanol and the cyclopropylcarbinol functionalities at the C/D ring moiety is quite unusual. Various fatty acid esters of phorbol have been shown to be the active components responsible for the co-carcinogenic activity of croton oil. Esterification usually occurs at C(11) and C(12) with a pair of long chain and short chain fatty acids, as in the potent co-carcinogenic tetradecyl phorbol acetate (TPA).

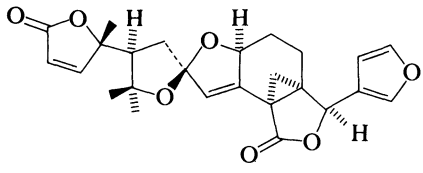


(14)

Recently a protein kinase (kinase C) has been suggested as the intracellular target of TPA, which may be a structural mimic of an endogenous kinase activator, namely diacylglyceride[35]. Other examples include glabretal (**15**)[36], a pentacyclic triterpenoid isolated from the heartwood of *Guarea glabra*, and cneorin C (**16**), the bitter principle of *Neochamaelea pulverulenta* (or *Cnenorum pulverulentum*)[37–39].



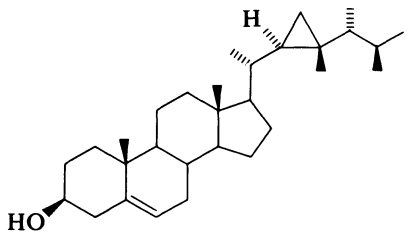
glabretal (**15**)



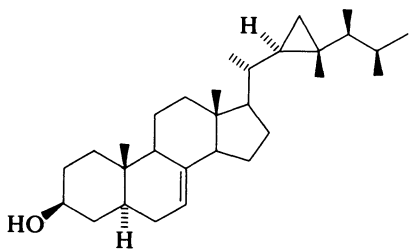
cneorin C (**16**)

6. Steroids

Steroids containing cyclopropyl groups in the side chain, as exemplified by gorgosterol (**17**) from the gorgonia *Plexaura flexnosa*[39] as well as the zoanthid *Palythoa* sp.[40],

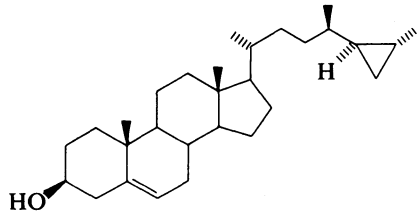


gorgosterol (**17**)

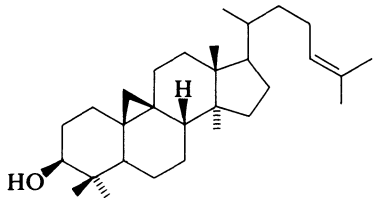


acansterol (**18**)

acansterol (**18**) from *Acanthaster planci*[41] and petrosterol (**19**) from the marine sponge *Petrosia ficiformis*[42] are commonly detected marine metabolites while the C-ring fused cycloartenol (**20**) is a major plant sterol. The biosynthetic assembly of the cycloartenol three-membered ring will be analyzed later in this chapter.



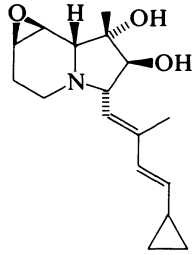
petrosterol (**19**)



cycloartenol (**20**)

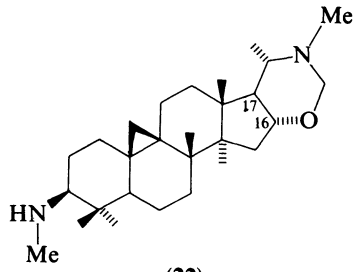
7. Alkaloids

The unusual indolizidinediol (**21**) with an $\alpha,\beta:\gamma,\delta$-unsaturated cyclopropyl side chain has been isolated from a *Streptomyces* species NCIB 11649[43]. This compound shows non-selective immunostimulatory properties. Furthermore, its acetate causes a reduction in frequency of beats of cultured heart cells, an effect often seen with certain β-blocking drugs.



(**21**)

Buxozine-C (**22**) was isolated from *Buxus sempervirens* L.[44]. It is the first buxus alkaloid having a tetrahydrooxazine heterocycle fused in positions 16_α, 17_β of the steroid backbone.

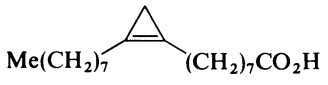


(**22**)

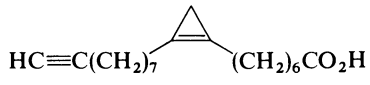
8. Cyclopropene-containing compounds

Cyclopropene-containing compounds are much rarer metabolites but a few well-characterized examples are known. It is likely they arise biogenetically from acetylenic precursors (themselves derived from olefins)[45]. Sterculic acid (**23**)[46] has been isolated from

the seed oil of *Sterculia foetida*. This compound and malvalic acid, a C_{18} analogue, have been found widely in various species of Malvales. Sterculinic acid (**24**), the first fatty acid to have both an acetylene and a cyclopropene ring, was found in *Sterculia alata*[46]. The feeding of sterculia oil, sterculic acid itself, or malvalic acid to hens causes discoloration of eggs, cessation of egg production and suppression of the hatching ability of the eggs[47].

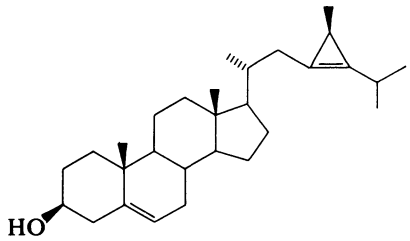


sterculic acid (**23**)



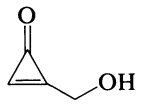
sterculinic acid (**24**)

Calysterol (**25**) is a C_{29} cyclopropene-containing marine sterol isolated from the sponge *Calyx nicaensis*[48]. The presence in calysterol of a cyclopropene ring suggests that in marine organisms sterols with unusual side chains may be quite widespread.



(**25**)

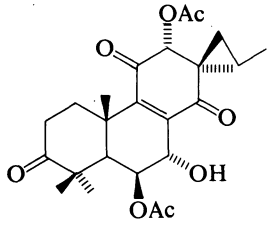
Even rarer still are cyclopropenones. A recent report on a labile antibiotic penitricin (**26**) revealed it has the indicated cyclopropenone structure[49]. Its mode of action is not yet known but it is doubtless an alkylating agent.



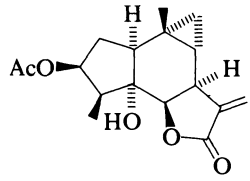
(**26**)

B. Classification by Substitution Patterns

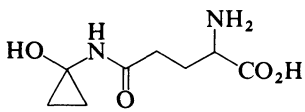
The above brief survey gives a sampling of the structural types of natural metabolites where cyclopropyl substituents have been observed. An alternative mode of initial classification is according to the substitution patterns on the cyclopropyl group. Common patterns include 1,2-dialkylation, such as in dictyopterene B (**1**), lactobacillic acid (**4**), coronamic acid (**8**), and petrosterol (**19**). The 1,1,2-trialkylation patterns are exemplified in gorgosterol (**17**), barbatusin (**27**)[50] and ivaxillin (**28**)[51]. The 1,1,2,2-tetrasubstitution occurs in marasmic acid (**13**), glabretal (**15**), and buxozine C (**22**), while the 1,2,3,3-tetrasubstitution has been illustrated above by pyrethrin (**11**), sirenin (**12**), and phorbol (**14**). The toxin coprine (**29**)[52] which contains a cyclopropanone hemiaminal moiety will be discussed further in Section IV. The substitution patterns often reflect and constrain modes of biosynthesis of the cyclopropane. Other known substitution patterns include the monoalkylation with heteroatom substitution as in 1-aminocyclopropane-1-carboxylic



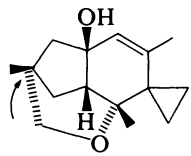
barbatusin (**27**)



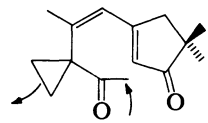
ivaxillin (**28**)



coprine (**29**)

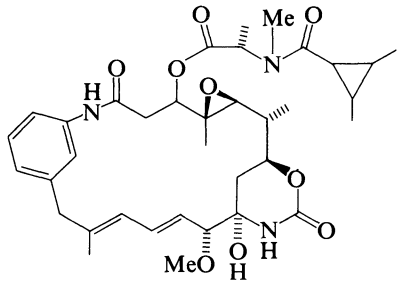


broderol (**30**)



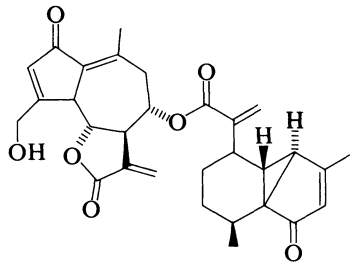
hypacrone (**31**)

acid (**9**), the 1,1-dialkylation as in broderol (**30**)[53], and hypacrone (**31**)[54], and the 1,2,3-trialkylation patterns are known as in ambruticin (**10**), normaytancypine (**32**)[55] and

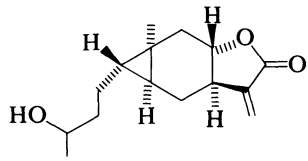


normaytancypine (**32**)

calysterol (**25**). The following two compounds, **33**[56] and **34**[57], are tetraalkylated. Finally, we note crispatene (**2**) has a pentaalkylated substitution pattern.



(**33**)



(**34**)

This initial survey of naturally occurring cyclopropanoid metabolites raises several questions relating to the biochemistry including function and metabolism of the compounds and in particular the cyclopropyl group. In the bulk of this chapter we summarize what evidence is available on modes of biosynthesis and degradation of cyclopropyl substituents. While in several cases, e.g. in terpenoids and steroids of the cycloartenol (**20**) case, biogenetic tracer studies or stereochemical probes have been carried out and are quite revealing about precursor–product relationships, there are very few cases indeed where specific enzymatic catalysts have been identified, isolated, and characterized for action on specific cyclopropane substrates.

Thus, much of the Section II and III outlines reasonable mechanistic proposals of biological routes to cyclopropyl group construction and degradation. However, in most cases, little intimate mechanistic knowledge is available to constrain speculation. Notable exceptions are in lactobacillic acid (**4**) metabolism and ACPC (**9**) processing in bacteria. The last section (IV) of this chapter will analyze a distinct aspect of cyclopropanoid biochemistry, cases where the cyclopropyl group is used as a probe of mechanism, sometimes diagnostic of radical intermediates and sometimes functioning in specific mechanism-based inactivation of target enzymes.

C. Cyclopropyl Groups as Transient Structural Elements in Metabolic Processing

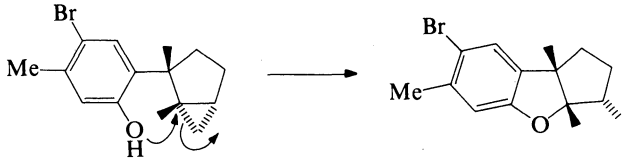
Most of the compounds cited in this introductory section are produced in metabolic processes where the cyclopropane-containing metabolite appears to be the stable end product or secondary product with as yet unobvious metabolic function. However, this is not the case in at least two types of systems, in which cyclopropyl species are key and necessary intermediate structures in high flux metabolic pathways. The first example is the squalene (**76**) and phytoene (**88**) biosynthesis where presqualene pyrophosphate (**77**) and prephytoene pyrophosphate (**89**) are obligate cyclopropanoid intermediates in the net head-to-head condensations of two farnesyl pyrophosphate (**73**) or two geranylgeranyl pyrophosphate (**66**) molecules respectively. The second example is in plant hormone metabolism where C(3) and C(4) of the amino acid methionine are excised as the simple hormone ethylene via intermediacy of 1-aminocyclopropane-1-carboxylic acid (**9**). Both examples will be discussed in detail in the Section II.

In addition to these two well-documented cases of cyclopropyl species as well-defined metabolic intermediates, we note below three examples where a cyclopropyl structure is strongly implicated as a precursor to a subsequent metabolite.

1. Laurinterol to aplysin

Although the majority of the marine molluscs have protective outer shells, a subclass of the molluscs, the opisthobranchs (Opisthobranchia), are lacking the characteristic external shell but frequently possess the ability to use toxic and/or noxious organic compounds as defensive agents. For example, studies of the digestive gland components of the herbivorous sea hare *Aplysia kurodai* resulted in the isolation of a brominated compound aplysin (**35**)[58]. The apparent lack of significant predators of sea hares might be due to its ability to produce this defensive chemical aplysin (**35**). Further investigation of *Aplysia* species have confirmed a distinct feeding preference for the brown red algae of the genus *Laureneia*[59]. Since a related compound, laurinterol (**36**), has been found in *L. intermeda* and *L. glandulifera*[60], and laurinterol (**36**) can be converted to aplysin (**35**) by treatment with *p*-toluenesulfonic acid, formation of aplysin (**35**) in the sea hares is thus considered to be derived from laurinterol (**36**)[61]. This example not only nicely demonstrates the crucial

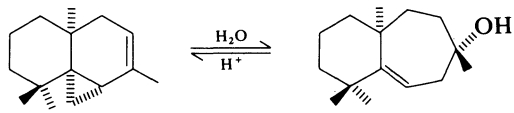
role of a cyclopropane-containing compound in the biosynthesis of an important metabolite, but also exemplifies the defensive strategy taken by some molluscs by utilizing compounds produced by marine algae and concentrated in the animal through intensive grazing[62]. Whether the conversion of ingested laurintenol (**36**) to aplysin (**35**) is indeed *enzyme*-catalyzed by an *Aplysia* enzyme is as yet unproven.



laurinterol (**36**) aplysin (**35**)

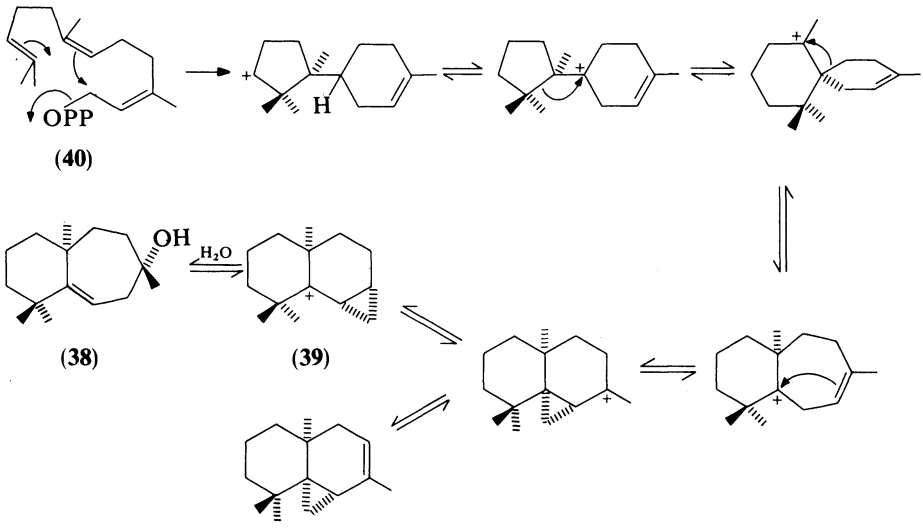
2. *Thujopsene to widdrol*

(−)-Thujopsene (**37**), a sesquiterpene containing an olefinic linkage conjugated with a cyclopropane ring, was isolated from wood oil of *Thujopsis dolabrata*[63] and was later found in cedarwood oil[64]. It also occurs widely in the oils of Cupressales[65, 66]. Under mild acid conditions (0.02 M $HClO_4$ in dioxane), thujopsene was shown to rearrange with



thujopsene (**37**) widdrol (**38**)

retention of the stereochemical integrity of the cyclopropylcarbinyl group into the naturally occurring widdrol (**38**)[67]. This reversible transformation has been shown to



(**40**)

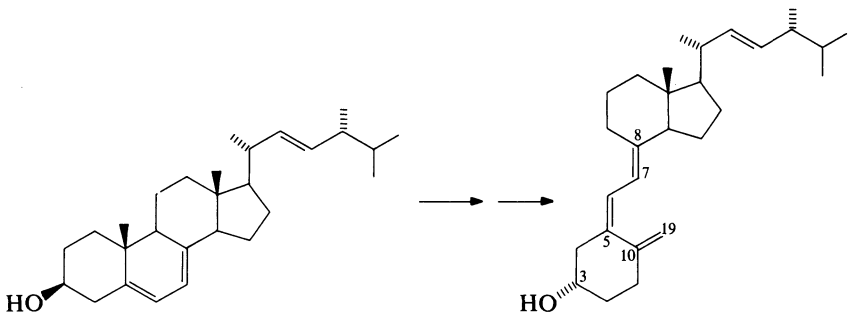
(**38**) (**39**)

(**37**)

proceed with the formation of the cyclopropylcarbinyl cation which by direct interconversion or by a series of 1,2-bond shifts yields (**39**), the direct precursor of widdrol (**38**)[68]. This mild and well-documented rearrangement starting from the cyclization of farnesyl pyrophosphate (**40**) is believed to be the pathway occurring *in vivo*, but again the question of which steps (after the first) in the sequence may be enzyme-catalyzed and which may be non-enzymatic rearrangements (if any) is not yet known.

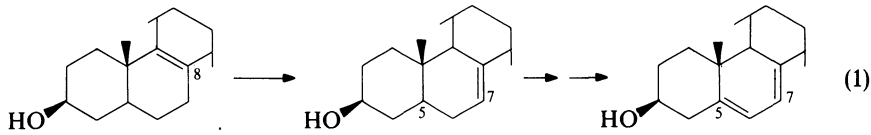
3. Ergosterol construction of the 5,7-diene unit

Ergosterol (**41**), a plant sterol, is the key precursor of vitamin D_2 (**42**) (ergocalciferol). Biosynthesis of vitamin D_2 (**42**) proceeds via a photochemical cleavage of the B ring of ergosterol (**41**) to form 9,10-secoergosterol followed by a thermal 1,7-sigmatropic shift.



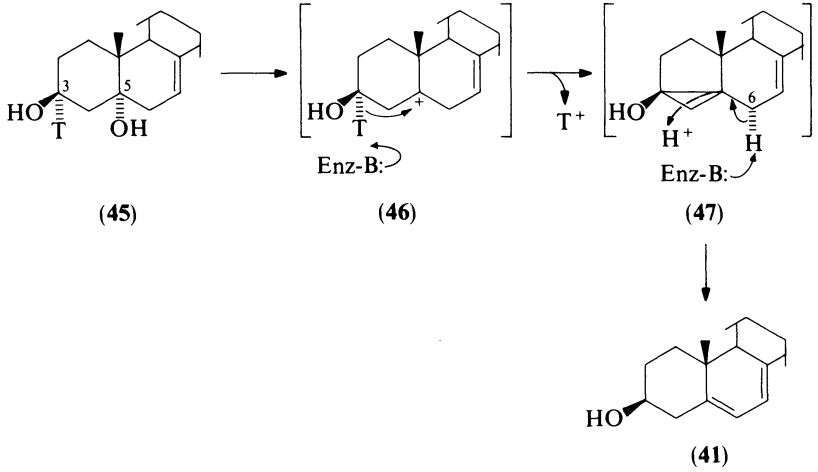
ergosterol (**41**) vitamin D_2 (**42**)

Formation of the physiologically crucial $\Delta^{5,7}$-diene in the B ring of ergosterol (**41**) has been suggested to arise from 5α-ergosta-8(9), 22-dien-3β-ol (**43**) via $\Delta^8 \rightarrow \Delta^7$ isomerization to (**44**)



(**43**) (**44**) (**41**) (1)

and net C(5,6)-dehydrogenation[69–71] (equation 1). Studies of ergosterol (**41**) biosynthesis in the yeast *Saccharomyces cerevisiae* led to the isolation of strains containing single gene mutations which are devoid of functional enzymes required for the essential isomerization and dehydrogenation[72]. Although the exact mechanism of introduction of the $\Delta^{5,6}$-bond during ergosterol biosynthesis is still uncertain, the possible involvement of C(5)-oxygenated intermediates has been proposed. The incorporation of ergosta-7,24(28)-dien-3β-ol (**44**) into ergosta-7,22-dien-3β,5α-diol (**45**) by aerobically growing *S. cerevisiae*[73] and other feeding experiments provide the evidence for the participation of a C(5)-oxygenated intermediate, since the later sterol has been previously shown to be efficiently converted by *S. cerevisiae* into ergosterol (**41**) under aerobic conditions[74]. A mechanism shown in the following equation (2) has been proposed to account for the loss of the 3α-tritium label from [3α-$^3H_1$]ergosta-7,22-dien-3β,5α-diol (**45**) upon its conversion into ergosterol (**41**) by a partially purified yeast enzyme[75]. Generation of a cyclopropane intermediate (**47**)



(45) (46) (47) (41) (2)

after loss of the C(5)-OH as H_2O would explain the cleavage of the C(3)–T bond. The subsequent abstraction of the 6α-H initiates the formation of the Δ^5-double bond and also induces the regiospecific cyclopropane opening as well as the stereospecific reprotonation at C(3) with net retention by a solvent-derived proton. Alternative mechanisms involving oxidation of the 3-ol to a ketone followed by reduction are precedented for NAD-containing enzymes but lead to net conservation of the tritium via its quantitative delivery back on regeneration of the 3β-ol. If the cyclopropanol intermediate is indeed formed in this 5,7-diene biosynthesis it probably remains enzyme-bound until its forward conversion to ergosterol.

II. BIOLOGICAL ROUTES TO CYCLOPROPYL GROUP CONSTRUCTION

In this section we will examine the known routes of biosynthetic formation of cyclopropyl groups with attention directed to how the carbon–carbon bond is constructed. A major division is apparent at the outset between those cases where the cyclopropane is fashioned by skeletal rearrangement of the existing carbon framework from those cases where the apical CH_2 moiety of a cyclopropyl group is introduced as an external one-carbon fragment from *S*-adenosylmethionine via the addition to an olefinic precursor.

First, we will take up cyclopropyl group formation by the rearrangement of carbon skeletons via cationic intermediates encountered in various mono- and sesquiterpenes, and also examine the illudin biosynthesis where contraction of a cyclobutyl cation to a cyclopropane has been invoked. We will then discuss the head-to-head condensation of isoprenoid alcohols at the C_{15} or C_{20} level to generate the cyclopropyl intermediates, presqualene pyrophosphate and prephytoene pyrophosphate, on the way to the C_{30} and C_{40} polyene hydrocarbons, squalene and phytoene respectively. Conversion of 2,3-oxidosqualene via common intermediate protosterol cation to cycloartenol or lanosterol represents an important pathway in which the angular methyl group participates in the three-membered ring formation. The cyclopropanation outcome of this process has been carefully studied.

The net addition to an olefin moiety of a bridging methylene group derived from the activated methyl fragment of *S*-adenosylmethionine commonly occurs in the biosynthesis of cyclopropane-containing steroidal side chains and fatty acids, and has been best studied

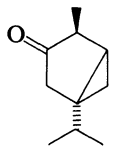
in lactobacillic acid formation catalyzed by a bacterial cyclopropane synthetase. An alternate route for conversion of a portion of *S*-adenosylmethionine arises in the biotransformation of the four-carbon methionyl chain into l-aminocyclopropane-l-carboxylic acid (**9**) mediated by a coenzyme B_6-dependent catalyst. This is a formal internal γ-replacement reaction.

Last, we shall note evidence for biological cyclopropane formation by photochemical processes found in crispatene biosynthesis.

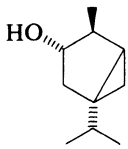
A. Cyclopropane Formation by Skeletal Rearrangement of Carbon Framework

1. Biosynthesis of thujane-type monoterpenes

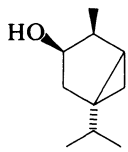
3-Thujone (**48**), 3-isothujone (**51**), the corresponding alcohols (**49**, **50**, **52**, **53**) and the olefin α-thujene (**54**) are the most prominent members of the thujane family which is a



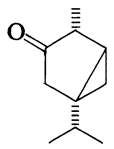
d-3-thujone (**48**)



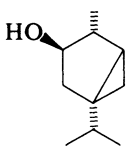
d-3-thujanol (**49**)



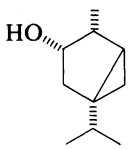
d-3-neothujanol (**50**)



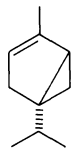
l-3-isothujone (**51**)



l-3-isothujanol (**52**)

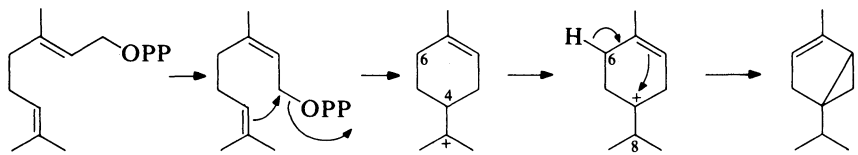


l-3-neoisothujanol (**53**)



l-α-thujene (**54**)

common bicyclic monoterpene present in a wide variety of plants. Formation of the thujane skeleton is considered to be a consequence of an initial cyclization of the C_{10} acyclic isoprenyl pyrophosphate precursor (**59**), followed by the loss of a proton from C(6) to form the C(1,6)-double bond and the cyclopropane ring with a 1,2-hydride shift from

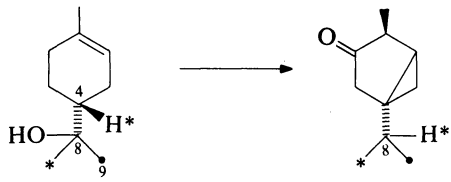


(**59**) (**60**) (**54**)

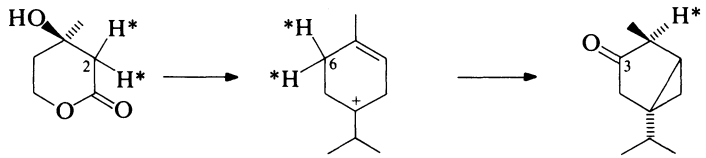
(3)

C(4) to C(8) (equation 3). The *in vivo* labeling patterns[76,77] of *d*-3-thujone (**48**), sabinene (**55**) and other thujane-type monoterpenes derived from [2-^{14}C]mevalonic acid (**56a**) in various species are consistent with Ruzicka's hypothesis[78] in which the double bond of the

hypothetical monocyclic intermediate is involved in the formation of the cyclopropane ring. Using specifically labeled α-[4-^{3}H,10-$^3H_3$,9-^{14}C]terpineol (**57**) and [2-$^3H_2$,2-^{14}C]mevalonic acid (**56b**) as exogeneous precursors in *Tanacetum vulgare*, Banthorpe and his coworkers demonstrated, as expected, that two hydride shifts, one from C(4) (probably pro-S hydrogen) to C(8) and one from C(6) to C(1), occur during the biosynthesis of *d*-3-thujone (**48**)[79,80]. Based on their observations, a possible pathway for *d*-3-thujone

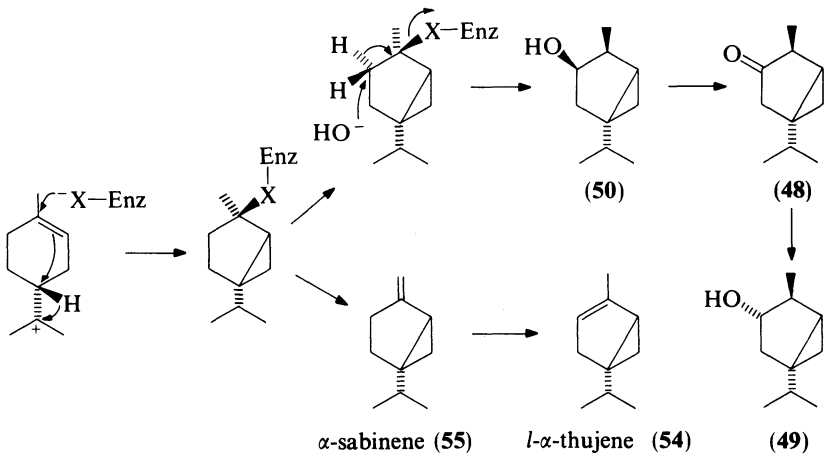


(**57**) (**48**)



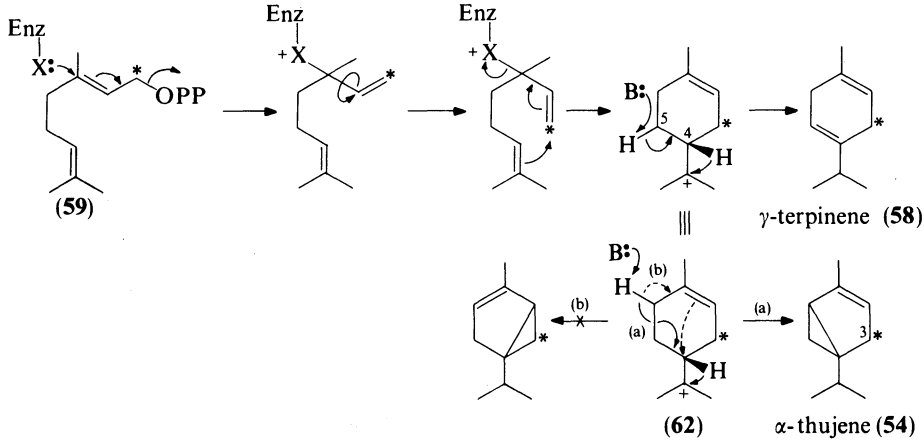
(**56b**) (**48**)

formation by way of *d*-3-neothujanol (**50**) was proposed. The 1,2-hydride shifts at the two sites are net intramolecular and occur either directly or perhaps by $NAD^+/NADP^+$ dependent reversible transfer within a compartmentalized system. This scheme suggests the introduction of oxygen during the cyclization step of a C_{10} acyclic precursor and could



also account for the formation of α-sabinene (**55**) and 1-α-thujene (**54**) which often concur with other thujane monoterpenes. Since sabinene (**55**) rather than the normal product 3-thujone (**48**) accumulated in tissue cultures of *Tanacetum vulgare*[81] and photooxidation of the olefin did afford oxygen functionality on C(3)[82], formation of C(3)-oxygenated thujane monoterpenes via sabinene (**55**) has also been suggested. Supporting

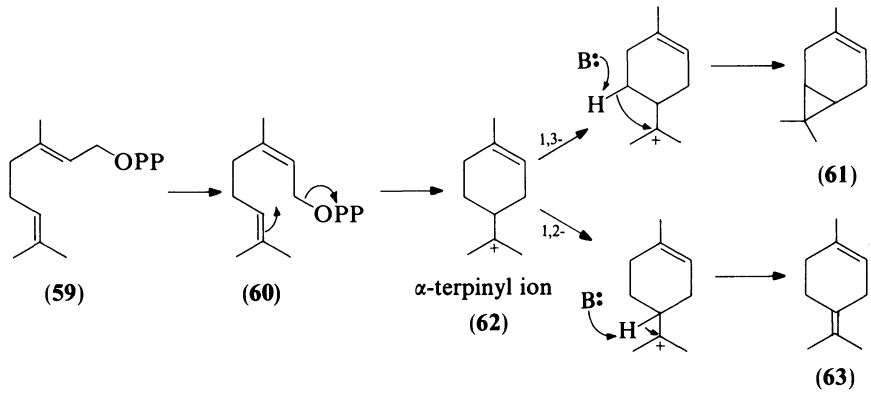
evidence for the intermediary role of sabinene (**55**) had been provided by Karp and Croteau[83] who had observed that at reduced oxygen levels, label from geraniol accumulated in the olefin sabinene, while much less sabinyl acetate and 3-thujone (**48**) were formed in *Artemisia absinthium* L. leaves. Other enzymatic studies of the biosynthesis of thujane-type monoterpenes include the conversion of neryl pyrophosphate (**60**) and geranyl pyrophosphate (**59**) to sabinene by a cell-free extract from the leaves of *Citrus limonum*[84] and the formation of *cis*-sabinene hydrate by a soluble enzyme preparation from *Majorana hortensis*[85]. Little is known about these enzymes, although their gross properties such as requirement for divalent metal ion and inhibition by sulfhydryl-directed reagents resemble other monoterpene cyclases or synthetases. It was thus presumed that the same mechanism was followed by these enzymes in which the double bond of the α-terpenyl intermediate, as in other cases, participates in the formation of the cyclopropane ring. However, Croteau and his coworkers have recently demonstrated that this hypothesis is not always tenable. Their observations were based on the α-thujene (**54**) formation catalyzed by a partially purified enzyme isolated from *Thymus vulgaris*[86]. This enzyme, γ-terpinene synthetase, has a molecular weight of 96 000 daltons, shows a pH optimum at 6.8, requires Mg^{2+} for catalytic activity, and can be inhibited by sulfhydryl-directed reagents and pyrophosphate. It catalyzes the formation of γ-terpinene (**58**) via the cyclization of the acyclic precursor, loss of a proton from C(5) to form the C(4, 5) double bond and a 1,2-hydride shift from C(4) to C(8). An offshoot of this hydride shift, coupled to loss a proton from C(6) and cyclopropane ring formation would generate α-thujene (**54**). The facts that α-thujene (**54**) is a minor product of this enzymatic reaction and that ^{3}H-labeling derived from [1-^{3}H]-geranyl pyrophosphate (**59**) and [1-^{3}H]neryl pyrophosphate (**60a**) is located specifically at C(3) of α-thujene (**54**) clearly indicated that the cyclopropane ring formation, at least in this case, is not coupled to or involved with a double bond rearrangement.



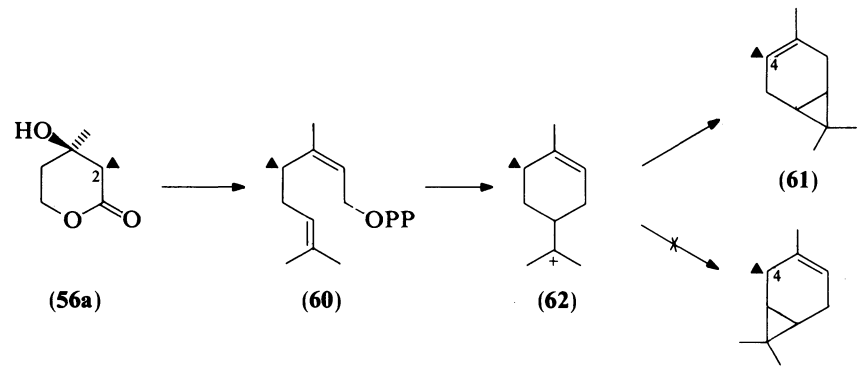
2. *Biosynthesis of carane*

The only commonly occurring bicyclic monoterpene with the carane skeleton is car-3-ene (**61**) which is believed to be formed by a 1,3-elimination from the α-terpinyl ion intermediate (**62**)[78]. The coexistence in many plants of car-3-ene (**61**) and α-terpinolene (**63**), thought to be derived from the same intermediate (**62**) as well via a 1,2-elimination, seems to support this hypothesis. However, degradation studies of α-car-3-ene (**61**) derived from

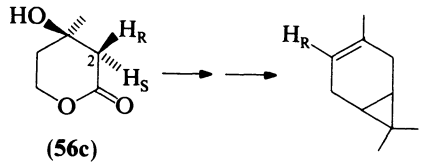
car-3-ene (**61**) terpinolene (**63**)



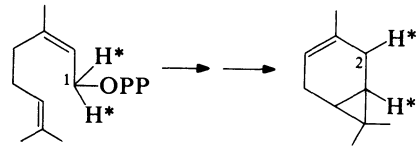
[2-^{14}C]-mevalonic acid (**56a**) in *Pinus palustris* or *P. sylvestris* showed that the ^{14}C-labeling is predominantly at C(4)[87]. Namely, the C(4) of the monoterpene is derived from C(2) of mevalonic acid (**56**) rather than C(4) as had been assumed and therefore, the cyclopropane ring formation must be accompanied by a double bond migration if α-car-3-ene (**61**) is indeed dervied from α-terpinyl ion (**62**) or its biosynthetic equivalents.



It was also shown in the same study that the pro-2*S* hydrogen of mevalonic acid (**56c**) is stereospecifically lost in the formation of Δ^3-double bond. Measurements of isotope ratios in car-3-ene (**61**) biosynthesized in *Pinus sylvestris* from [^{14}C,1-$^3H_2$]-nerol (**64**) had led to the finding of an unexpected 1,2-hydrogen shift, i.e. one of the C(1) hydrogens of nerol pyrophosphate (**60b**) is shifted to the site of the original double bond (C(2) of the product). Although a two-step mechanism was offered[88] for the cyclization in which enzyme-bound intermediates having active site nucleophile Y and/or Z incorporated are involved

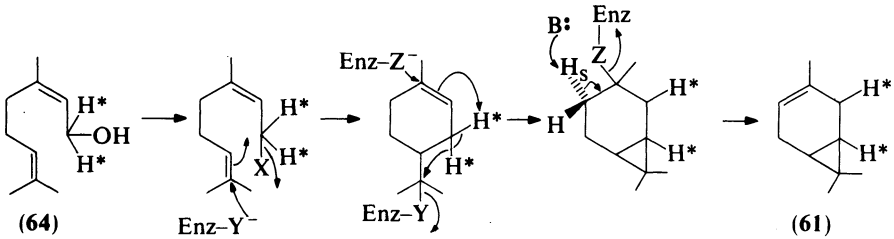


(56c)

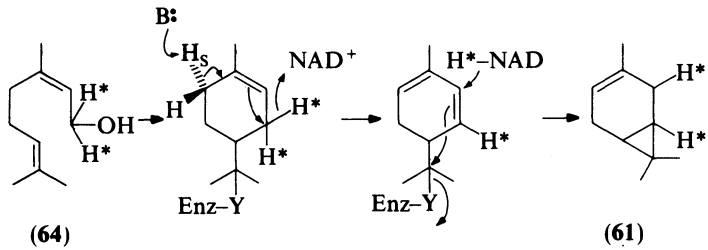


(60b)

(Scheme 1), an alternative pathway that requires reversible reduction/reoxidation with bound NAD(P)–NAD(P)H as outlined in Scheme 2 could also account for the experimental results.



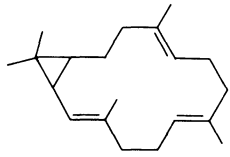
SCHEME 1



SCHEME 2

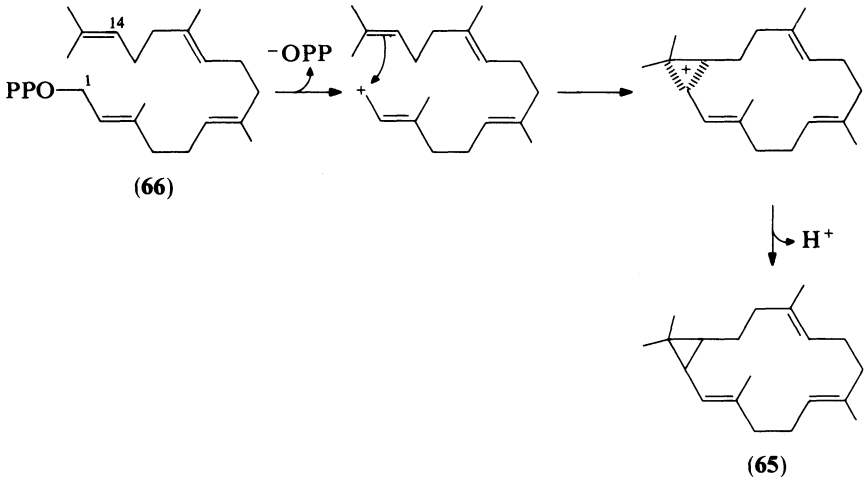
3. *Biosynthesis of casbene*

Casbene (**65**), an antifungal and antibiotic substance[89] produced from mevalonate (**56**) and then geranylgeranyl pyrophosphate (**66**), was first isolated from cell-free extracts of castor bean (*Ricinus communis*) seedlings[90,91]. It has been shown that casbene (**65**) serves as a phytoalexin for castor bean plant and thus, the biosynthetic activity to yield **65** (as a potential defense substance) can be greatly enhanced (20–40 fold) if the parent seedlings are exposed to potentially pathogenic fungi such as *Rhizopus stolonifer*, *Aspergillus niger*, or *Fusarium moniloforme*[89].



casbene (**65**)

A biosynthetic pathway involving intramolecular cyclization to form a non-classical carbocation (corner-protonated cyclopropane) or its equivalent between C(1) and the terminal 14,15-double bond of geranylgeranyl pyrophosphate (**66**), followed by proton elimination from the original C(1) to yield casbene (**65**) with its fused cyclopropane and macrocyclic ring system, has been proposed (equation 4)[91, 92]. This process is mechanisti-



(**66**)

(**65**)

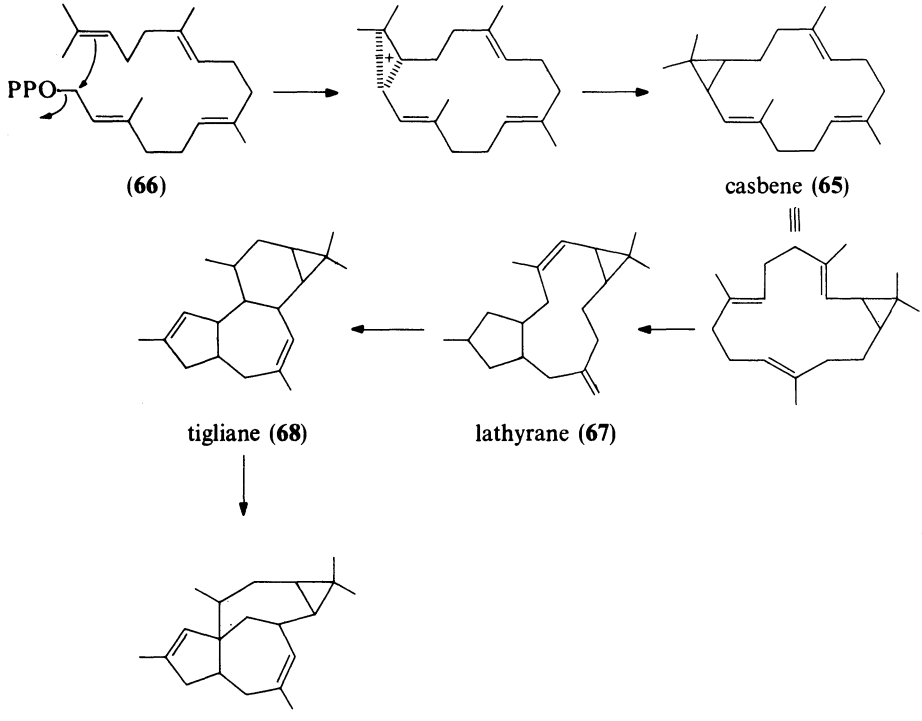
(4)

cally analogous to the condensation steps in the formation of presqualene (**77**) and prephytoene pyrophosphate (**89**) which will be discussed later in this section. Casbene has also been suggested to be the immediate precursor in the biosynthesis of a number of polycyclic diterpenes, such as lathyrane (**67**), tigliane (**68**) and ingenane (**69**)[92, 93], many of which contain a cyclopropane ring with a gem-dimethyl group fused to a large ring.

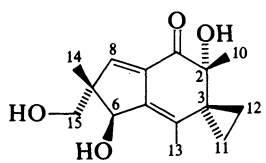
Casbene synthetase has been partially purified from extracts of castor bean seedlings infected with a fungus[94]. This single chain peptide has a molecular weight of ca. 53 000 daltons, and requires no cofactors but a divalent metal ion. Magnesium ion is most effective, whereas manganese ion is inhibitory at concentrations above 0.2 mM. This enzyme is localized in proplastids in the castor bean tissue along with geranylgeranyl pyrophosphate synthetase after elicitation of casbene synthesis by exposure to fungus.

4. Biosynthesis of illudins

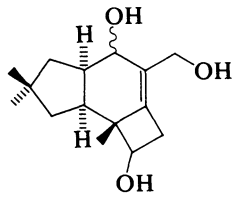
Illudin S (**70**) and illudin M (**71**) are two cyclopropane-containing toxins isolated from the bioluminescent mushroom *Clitocybe illudens*[95] or *Lampteromyces japonicus*[96, 97]. The



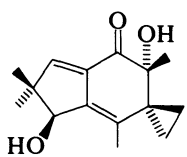
coexistence of illudol (**72**), a protoilludane metabolite, in the same fungus culture provides good evidence for the biogenetic origin of these unique sesquiterpenes.



illudin S (**70**)

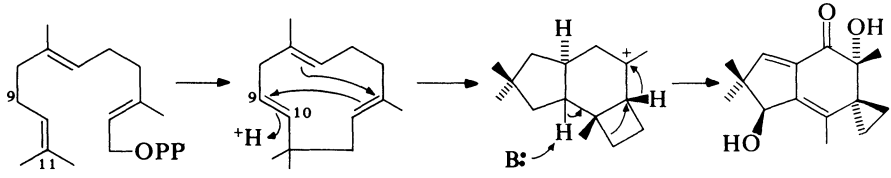


illudol (**72**)



illudin M (**71**)

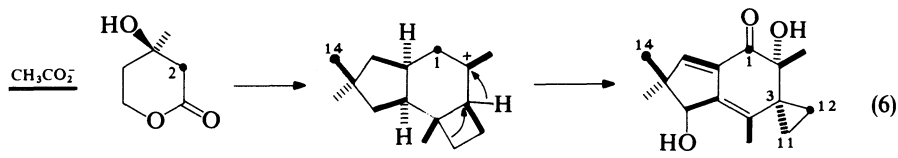
Studies of the precursor–product relationship in various biogenetically related humulene-derived metabolites have led to a unified scheme (equation 5) in which intramolecular cyclization of *trans,trans*-farnesyl pyrophosphate (**73**) generates humulene (**74**) by the attack at C(11) of the distal double bond and loss of a proton from C(9); reprotonation at C(10) of the key intermediate initiates further cyclization to a cyclobutyl-containing protoilludyl cation (**75**). Subsequent bond migration accompanied by contraction of the cyclobutane ring to the cyclopropane as shown, would then yield illudins. In accordance with the postulated pathway of illudin formation, C(1), C(14) and one of the



(73) humulene (74) protoilludyl cation (75) (71)

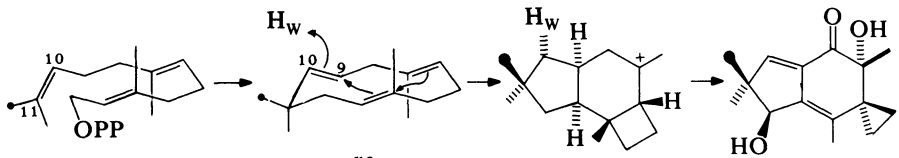
(5)

two cyclopropyl methylene carbons (in **71a**) were shown to be derived from C(2) of mevalonic acid (**56a**). In feeding studies with [1,2-$^{13}C_2$]acetate, other enriched carbons gave rise to six pairs of enhanced and coupled doublets as judged by ^{13}C-NMR[98]. The results of these two feeding experiments are summarized in the following equation (equation 6). Based on the observed derivation of C(14) of illudin S (**70**) and M (**71**) from



(56a) (75) (71a) (6)

C(2) of mevalonic acid (**56a**) as well as the known absolute configuration of illudol, the stereochemical outcomes of the early steps can be inferred (equation 7): farnesyl pyrophosphate (**73**) cyclization has occurred exclusively on the *si* face of the distal double bond; the humulene (**74**) cyclization must have occurred from the RSR-CT conformation; and protonation at C(10) has taken place at the *re* face of the 9,10-double bond[99-101].

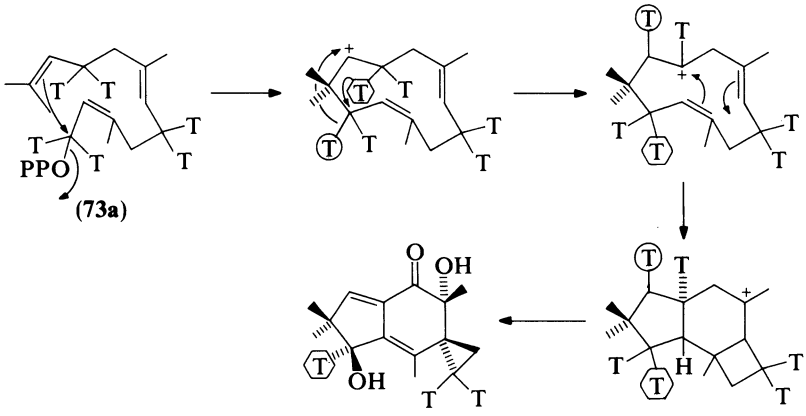


si (73) *re* RSR-CT (74) *cis* (75) (71)

(7)

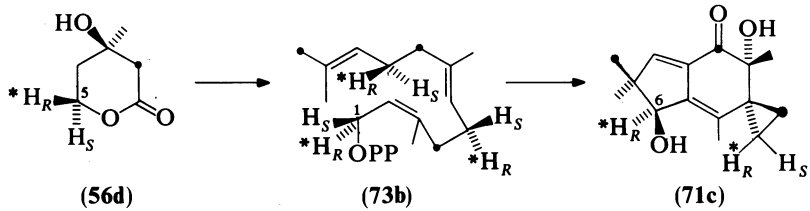
Since C(11), which is *cis* to the C(2) hydroxyl group as suggested by the greater upfield shift in the presence of Pr(fod-d_9)$_3$, is coupled to C(3), C(12) has been assigned as derived from C(2) of mevalonic acid (**56**)[102]. In order to account for these assignments the crucial cyclopropane ring formation step by cyclobutane ring contraction of a protoilludyl cation (**75**) requires a *trans*-1,2 Wagner–Meerwein rearrangement. This rearrangement would incorporate the carbon derived from C(2) of mevalonic acid into the methylene position of the cyclopropane that is *trans* to the C(2) hydroxy moiety. However, such a *trans*-1,2 Wagner–Meerwein rearrangement is unprecedented. Other unusual features concerning the biosynthetic formation of illudin type sesquiterpenes were found by Hanson and his coworkers in their incorporation studies of a series of tritiated precursors[103]. Illudin M

(**71b**) derived from (5*RS*)-[5-$^{3}H_2$,2-^{14}C]mevalonic acid (via **73a**) retained three tritium labels, two of which were located in the cyclopropane ring and the third at C(6) (equation 8)[104]. The origin of the label at C(6) had been established as 5-H_R of mevalonate based on



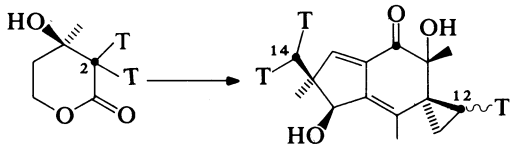
(**73a**) (**71b**) (8)

analysis of products (**71c**) isolated from incubations of (5*R*)-[5-$^{3}H_1$,2-^{14}C]mevalonic acid (**56d**) and all-*trans*-[1,5,9-$^{3}H_3$,4,8,12-$^{14}C_3$]-farnesyl pyrophosphate (**73b**). If the hydroxy at C(6) of illudin M (**71**) has been introduced with the usual retention of configuration[105], these results would imply that the initial cyclization of farnesyl pyrophosphate (**73**) has occurred with inversion of configuration at the C(1) carbinyl carbon. However, when (1*RS*)[1-$^{3}H_1$,2-^{14}C]farnesyl pyrophosphate was the precursor, no tritium labeling was found in the product illudin M. A series of hydride shifts was then proposed to account for these results as shown above (equation 8); however, these should



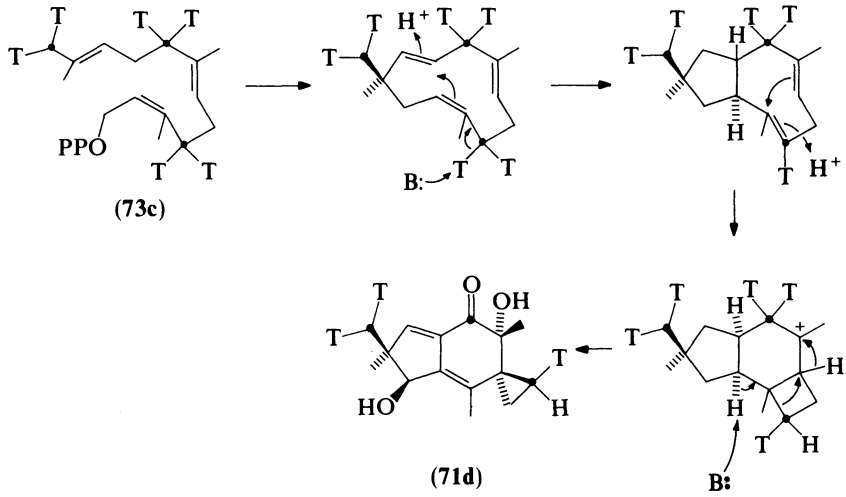
(**56d**) (**73b**) (**71c**) (9)

be considered still as speculations. Feeding of [2-$^{3}H_2$,2-^{14}C]mevalonic acid (**56b**) gave illudin M (**71d**) having two tritium atoms labeled at C(14), but only one tritum atom



(**56b**) (**71d**)

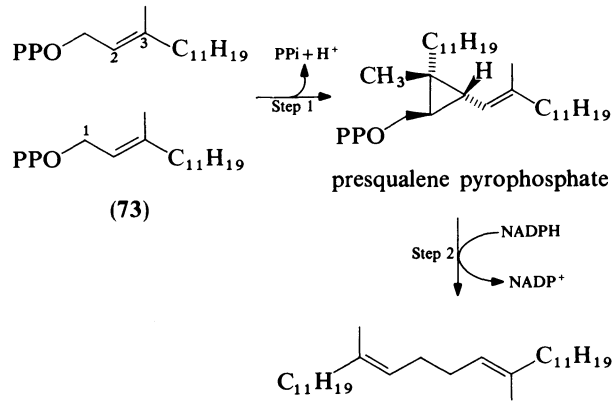
incorporated into the cyclopropane ring (probably at C(12))[106]. Similar results were obtained using [4,8,12-$^{3}H_{6}$,4,8,12-$^{14}C_{3}$] farnesyl pyrophosphate (**73c**) in which only 3.4 equivalents of tritium were retained (**71d**). The apparent loss of a [2-$^{3}H_{2}$]mevalonate label in the cyclopropane ring demands a modified mechanism (equation 10), possibly via a non-concerted cyclization of humulene to form the illudin skeleton.



(10)

5. *Presqualene pyrophosphate biosynthesis*

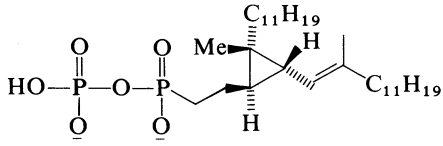
The common immediate precursor for the biosynthetic formation of cholesterol and triterpenes is squalene (**76**) which is derived from the head-to-head condensation of two molecules of farnesyl pyrophosphate (**73**) (equation 11)[107]. This is a complex reaction



(11)

catalyzed by a single enzyme requiring NADPH as the cofactor, emphasizing the reductive nature of the C(1) to C(1) joining. A discrete cyclopropane-containing intermediate is produced and then converted on to the acyclic C_{30} polyene (**76**). In a formal sense C(1) of

one molecule of farnesyl pyrophosphate (**73**) is inserted into the C(2,3) double bond of the second farnesyl pyrophosphate molecule with concomitant loss of one of the pyrophosphate groups and ejection of a proton to yield a C_{30} cyclopropyl pyrophosphate known as presqualene pyrophosphate (**77**). A reductive rearrangement of this key intermediate in the NADPH-consuming step results in the formation of squalene (**76**)[108-110]. The intermediacy of presqualene pyrophosphate (**77**) was first conclusively established by Muscio and coworkers[111]. Their results indicated that condensation to form presqualene pyrophosphate (**77**) proceeds in a much more rapid fashion than the overall squalene synthesis. A similar conclusion was reached by Corey and Volante[112] as well, who had demonstrated that a presqualene pyrophosphate analog with a C–P bond, presqualene



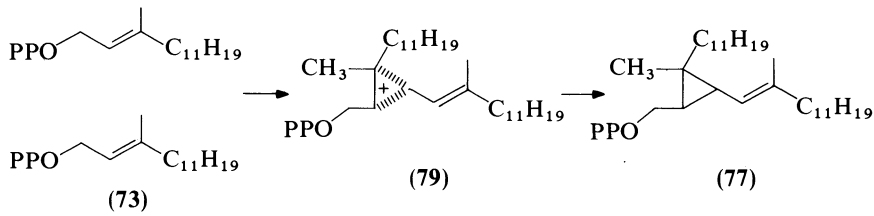
(**78**)

phosphonophosphate (**78**), inhibits squalene (**76**) formation but not presqualene pyrophosphate (**77**) synthesis from mevalonic acid (**56**). These results in conjunction with the observations made by Agnew and Popják[113] in which farnesyl pyrophosphate (**73**) inhibits the synthesis of squalene (**76**) and not presqualene pyrophosphate (**77**) at high concentrations of farnesyl pyrophosphate strongly suggested that at least two discrete catalytic events are involved and presqualene pyrophosphate exists as a free intermediate.

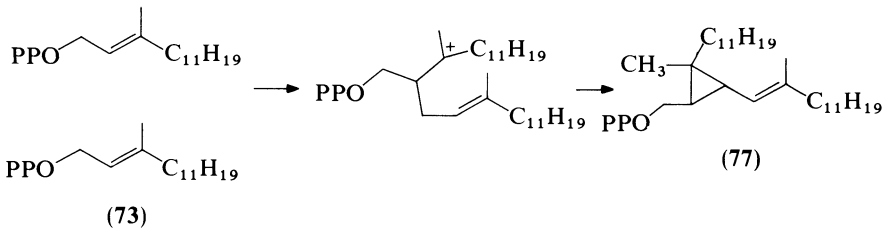
The enzyme squalene synthetase catalyzes the formation of squalene from farnesyl pyrophosphate and is a microsomal enzyme[114] which requires a divalent cation for both synthesis and forward conversion of presqualene pyrophosphate (**77**). Either NADH or NADPH can serve as a reductant for squalene synthesis. This enzyme can be solubilized from yeast microsomes with deoxycholate[115]. The specific activity of squalene synthetase after Amberlite XAD-2 and DEAE–cellulose chromatography as reported by Shechter and Block[115] was 1.5 nmol min^{-1} mg^{-1} with an overall 45-fold purification. The molecular weight was estimated to be 425 000 daltons. Although a different solubilization procedure was devised by Porter and his coworkers[116], and the purified enzyme with a specific activity of 20 nmol min^{-1} mg^{-1} in their preparation was claimed to be nearly homogeneous, several groups[114] have yet been unable to reproduce these results. Recently, new evidence provided by Agnew and Popják indicated that squalene synthetase is actually a relatively small microsomal enzyme with molecular weight of 55 000 daltons, and previous workers might have been working with aggregated proteins[117]. Although a ping-pong kinetic mechanism for squalene synthetase was once suggested by Beytia and coworkers[118] based on initial velocity patterns for product inhibition, this kinetic analysis had been criticized[114] since all the data were obtained with an enzyme–lipid dispersion and not the solubilized enzyme itself; the effective substrate concentration would be impossible to determine under such conditions. A non-Michaelis–Menten behavior was also found by Agnew and Popják[117] which further complicates the kinetic studies of squalene synthetase. Thus far, the bulk of the evidence indicates that squalene synthetase is probably a single enzyme with separate active sites for formation and breakdown of presqualene pyrophosphate (**77**), but the possibility that it is a tightly associated enzyme complex cannot be excluded.

In similarity to the biosynthesis of other cyclopropane-containing molecules, most mechanistic studies of squalene formation have been confined to chemical model systems and virtually no definitive experiments with the enzyme itself have been reported.

Nevertheless, a number of possible pathways which bear good chemical and/or biological analogies have been proposed. For example, presqualene pyrophosphate (77) could be formed via a protonated cyclopropane intermediate (**79**)[119] by direct electrophilic alkylation of the C(2,3) double bond (Scheme 3), or via a tertiary cation as suggested by



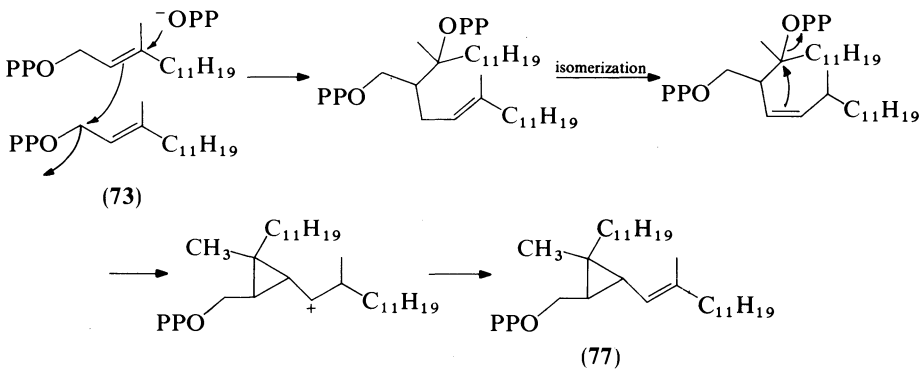
SCHEME 3



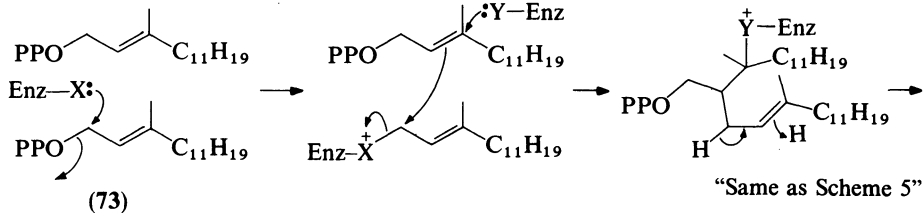
SCHEME 4

Altman and coworkers[120] (Scheme 4). Cyclopropane formation assisted by the participation of enzyme nucleophilic groups was proposed by van Tamelen and Schwartz[121] (Scheme 5), Beytia and coworkers[118] (Scheme 6), and the Utah group[122] (Scheme 7).

Reaction involving the formation of a sulfonium intermediate (**80**) followed by a sigmatropic rearrangement was formulated by Trost and Biddlecom[123] (Scheme 8) and cyclization initiated by an allylic copper carbenoid (**81**) was proposed by Cohen and coworkers[124] (Scheme 9). The common feature of all of these proposed mechanisms relies on the electrophilic addition of the donor to the acceptor prenyl pyrophosphate and is

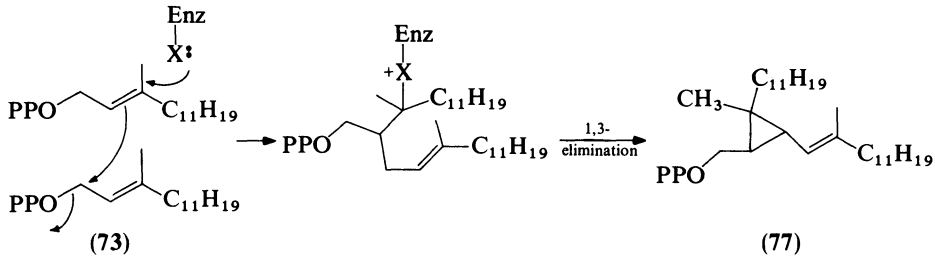


SCHEME 5



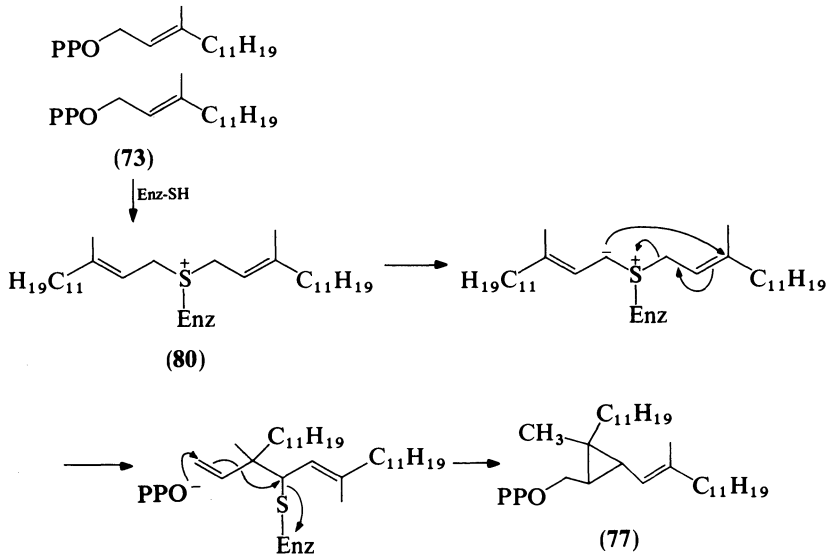
(73)

SCHEME 6



(73) (77)

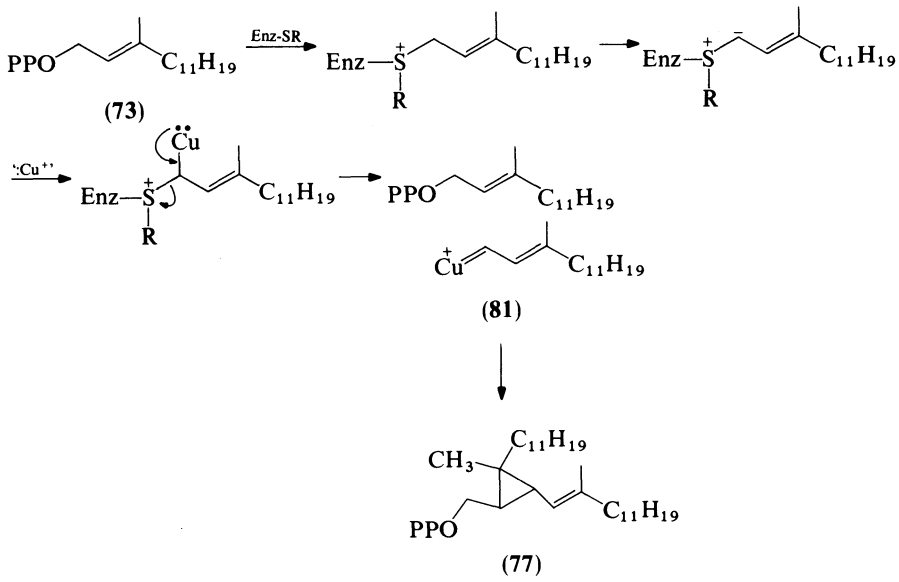
SCHEME 7



(77)

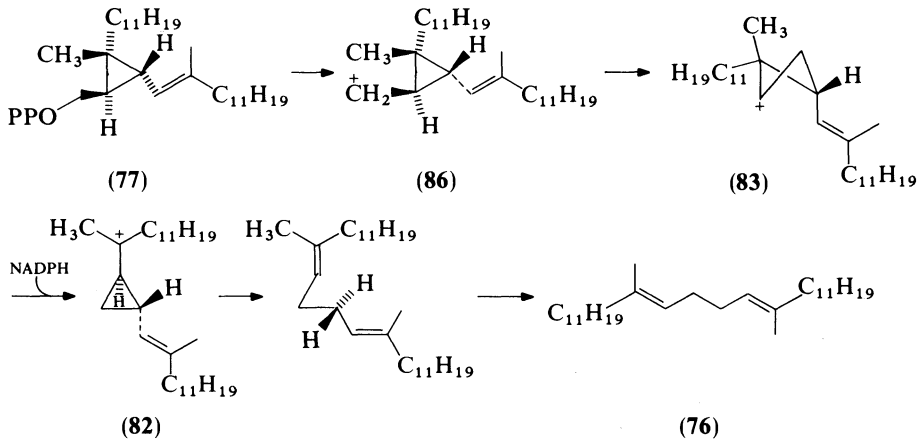
SCHEME 8

consistent with the finding[125] that electronegative substituents in the vicinity of the C(2,3) double bond of the donor substrate slow down or stop the reaction. However, it is questionable what relevance the very complex and often lengthy sequences have to the reaction pathway catalyzed by squalene synthetase. In contrast to the large number of



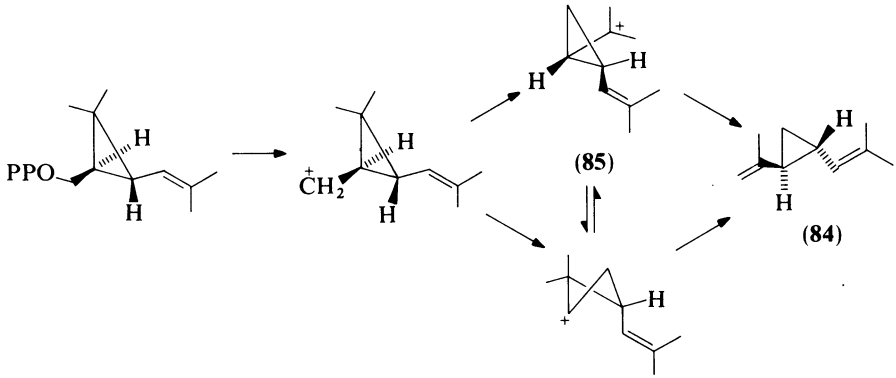
SCHEME 9

possible mechanisms proposed for the condensation process, only one likely pathway, based on the rearrangement of the cyclopropylcarbinyl cation (**82**) via a cyclobutyl cation (**83**) for the conversion of presqualene pyrophosphate (**77**) onto squalene (**76**) has been proposed (equation 12)[121, 122, 126].

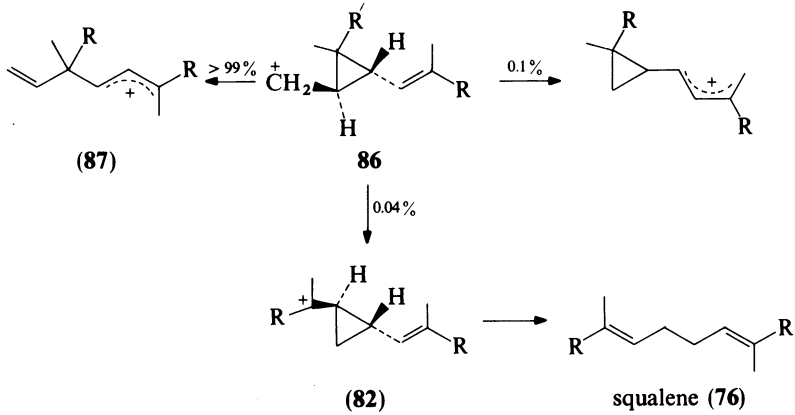


(12)

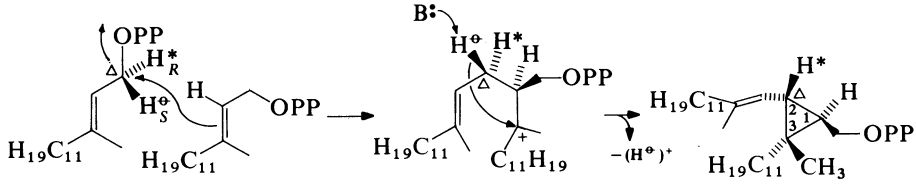
The recent discovery in *Artemisia tridentata rothrockii* of rothrockene (**84**)[127], a monoterpene that could be derived from the C_{10} equivalent (**85**) of the hypothetical tertiary cyclopropylcarbinyl intermediate (**82**) above, strengthens the suggestion of such carbocationic rearrangements in nature.



Since there are three possible ways to rearrange cyclopropylcarbinyl cation (**86**) of the type proposed in presqualene pyrophosphate conversion, and the unwanted cyclopropylcarbinyl (**86**) to allyl (**87**) rearrangement has been found to account for 99% of total reaction flux in model studies[127-131], squalene synthetase must exert strict regiochemical control in the catalytic steps to produce the enzymatic product squalene via the kinetically and thermodynamically unfavored (ca. 0.04% of the total non-enzymatic flux) rearrangement process (**86** → **82**). A tight enzyme–substrate complex that imposes an energy barrier



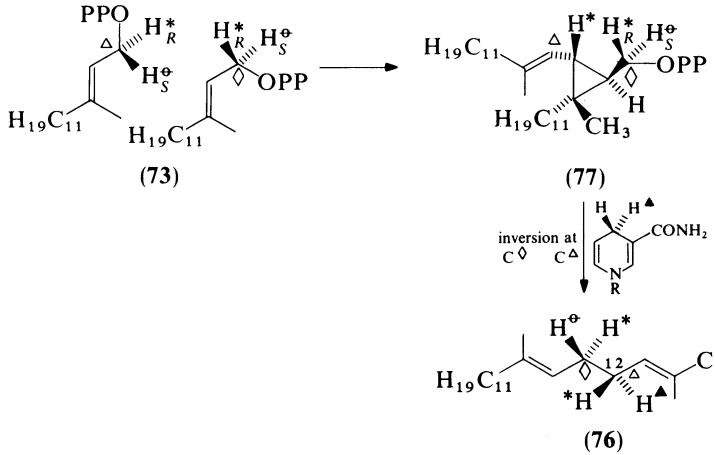
for the cyclopropylcarbinyl (**86**) to allyl (**87**) rearrangement by twisting the double bond was suggested by Coates and Robinson[131]. However, Poulter and his coworkers favor the notion that the electrostatic attractions of a tight ion pair between the cyclopropylcarbinyl cation (**82**) and pyrophosphate anion in a rigid environment could govern the regioselectivity of the rearrangement process[128, 132]. The pyrophosphate dependence of the binding of an ammonium analog that mimics the topological and electrostatic properties of the tertiary cyclopropylcarbinyl intermediate (**82**) seems to support the latter hypothesis[133]. Unlike mechanistic analysis of bond forming steps which have been hampered by the difficulty of obtaining highly active and homogeneous enzyme, the stereochemical outcomes of the squalene synthetase have been well characterized[134, 135]. During the initial coupling step in which C(1) of one molecule of farnesyl pyrophosphate is inserted into the C(2,3) double bond of the second molecule, the relative orientation of the



(73) inversion of C^{Δ} retention of C^{Δ} (77)

substituents on the C(2,3) double bond is retained and the alkyl group at C(3) of the cyclopropane ring is *trans* to the carbinyl carbon attached to C(1)[136, 137]. The absolute configuration of the three newly generated chiral cyclopropane centers was determined by Popják and coworkers to be 1*R*, 2*R*, 3*R*[138]. Of the two enantiotopic hydrogen atoms at C(1) of the prenyl donor, it was found that the hydrogen removed during the condensation process is the 1-H_{si}[139].

These results integrate into a clear picture in which the head-to-head coupling of two farnesyl pyrophosphate occurs at the 2-*si*,3-*re* face of the double bond of the prenyl acceptor, and the configuration of C(1) of the donor is inverted during the process. A more complex series of skeletal rearrangements is required to generate squalene (**76**) from

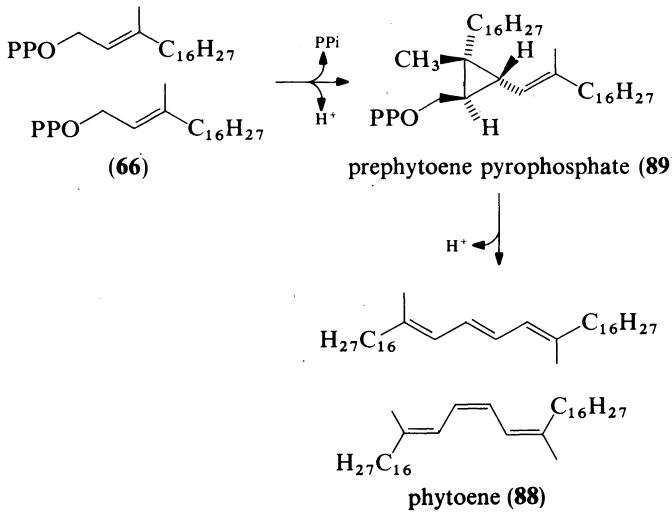


presqualene pyrophosphate (**77**). During this reductive cleavage step, both of the newly formed C(1,3) and C(2,3) cyclopropane bonds are cleaved and a new bond is introduced between the carbinyl carbon and C(3). These rearrangements lead to an inversion at the carbinyl carbon (C(1) of the prenyl acceptor) where the pyrophosphate is replaced[140]. A hydride transfer is needed for squalene formation; this hydride is donated from the 4-H_{si} position of the dihydropyridine ring[141] and ultimately occupies the pro-(12*R*) position in squalene[141].

6. Biosynthesis of phytoene

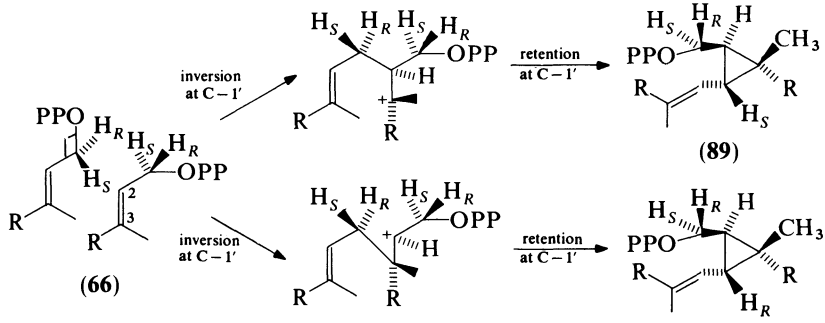
The carotenoids constitute a large group of naturally occurring pigments that are formed by the condensation of eight isoprenoid units. The key step in the biosynthesis of

carotenoids is the head-to-head coupling of two molecules of geranylgeranyl pyrophosphate (**66**) to form phytoene (**88**) (equation 13)[142]. This condensation leads to a cyclopropylcarbinyl pyrophosphate, prephytoene pyrophosphate (**89**), as the intermediate is analogous to the condensation of farnesyl pyrophosphate (**73**) to form squalene (**76**) catalyzed by squalene synthetase (equation 11). In the second step, however, there is no requirement for NAD(P)H and the phytoene (**88**) has an olefinic linkage joining the two C(1) carbons of the two C_{20} precursors (**66**).



(13)

The intermediacy of prephytoene pyrophosphate (**89**) was first shown by Altman and coworkers[126] who identified this compound as a product of the incubation of geranylgeranyl pyrophosphate (**66**) with an extract of photoinduced *Mycobacterium* sp. The direct incorporation of geranylgeranyl pyrophosphate (**66**) into phytoene (**88**) has been observed in various systems including a soluble tomato plastid enzyme system[143], chloroplasts isolated from *Phaseolus vulgaris*[144], cell-free extracts of *P. blakesleeanus*[142, 145, 146], and *Mycobacterium* sp.[147]. However, the only relatively well characterized enzyme system is isolated from the soluble fraction of acetone powder of tomato fruit plastids. The tomato plastid enzyme has been partially purified and carries out the direct conversion of both isopentenyl pyrophosphate[148] and geranylgeranyl pyrophosphate (**66**)[143] to phytoene (**88**). The molecular weight of phytoene synthetase was estimated to be 200 000 daltons[149].

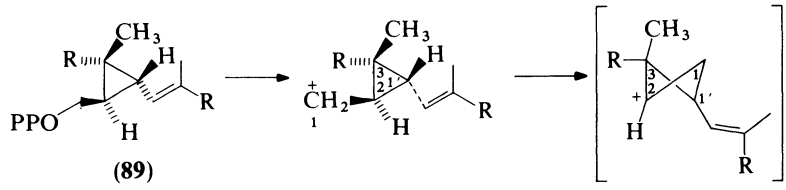


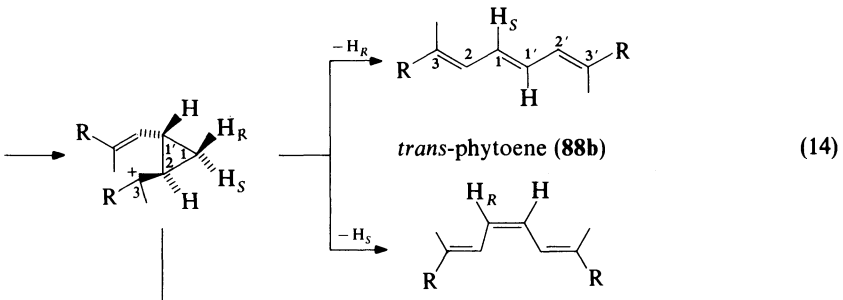
The only cofactor required for this condensation is a divalent cation, either Mg^{2+} or Mn^{2+}, and the activity can be inhibited by iodoacetamide, *N*-ethylmaleimide and *p*-hydroxymercuribenzoate. Cell-free extracts catalyzing phytoene formation have also been isolated from pea fruits[150], spinach leaves[151], *Mycobacterium*[147], *Halobacterium cutirubrum*[152], and fungi of *P. blakesleeanus*[145, 146, 153] and *N. crassa*[154–156]. However, these systems have not been studied in detail.

Formation of prephytoene pyrophosphate (**89**) might proceed, as proposed by Altman and coworkers[120], via a Mg^{2+}-assisted solvolysis of the pyrophosphate from C(1) of the prenyl donor with concomitant carbon–carbon bond formation between C(1) and C(2) as well as C(3) of the prenyl acceptor, or other mechanisms analogous to those proposed for presqualene pyrophosphate (**77**) formation. Although numerous chemical model studies have been reported, there is no conclusive evidence for enzymatic use of any of these mechanisms so far.

The subsequent ring cleavage reaction, if completely analogous to the reductive fragmentation step of squalene biosynthesis[130] in which NAD(P)H is an absolute requirement, would lead to the formation of lycopersene (**90**) (equation 16), the C_{40} homologue of squalene (**76**). However, the failure to observe the formation of lycopersene (**90**) in many *in vivo* and *in vitro* systems[157–161], and more directly, the NAD(P)H independence of this process[143, 148, 161–163] strongly argue against the intermediacy of lycopersene (**90**) in phytoene biosynthesis.

The condensation of geranylgeranyl pyrophosphate (**66**) may lead to the formation of 15-*cis*-phytoene (**88a**) or all-*trans*-phytoene (**88b**), depending on the stereochemistry of





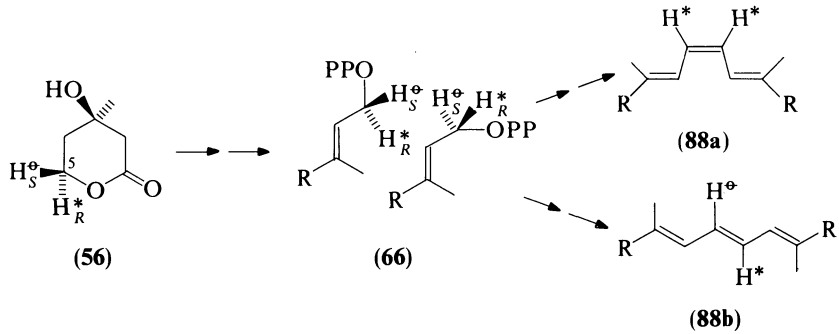
(14)

(15)

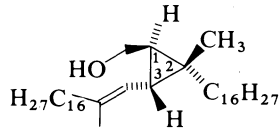
(16)

hydrogen removal. Extraction of H_R would lead to the formation of all-*trans*-phytoene (**88b**), whereas, removal of H_S would yield *cis*-phytoene (**88a**) as shown in equations 14 and 15 respectively. In the majority of cases that have been examined the end product is 15-*cis*-phytoene (**88a**). However, certain fungi and photosynthetic bacteria in the presence of inhibitors of dehydrogenation or under special conditions, will accumulate significant amounts of the all-*trans*-isomer (**88b**)[164–166]. A slight change of the disposition of the enzyme active-site base that is responsible for removing the diastereotopic proton might be sufficient to distinguish a *cis*-synthetase from a *trans*-synthetase[132].

The formation of phytoene (**88**) occurs with the stereospecific loss of one hydrogen from C(1) of each of the two geranylgeranyl pyrophosphate (**66**) molecules. Studies of the overall stereochemistry of this coupling reaction leading to the formation of *cis*-phytoene (**88a**) in tomatos[167], bean leaves[168], and *Phycomyces blakesleeanus*[163] show that both pro-*R* hydrogens from C(5) of mevalonate are retained at the central double bond. The two pro-*S* hydrogens are lost during this process. As expected, the phytoene generated from the *Mycobacterium* system which is known to synthesize *trans*-phytoene (**88b**), retains one pro-*S* and one pro-*R* hydrogen derived from C(5) of mevalonic acid (**56**)[163].



Samples of (1*R*, 2*R*, 3*R*) and (1*S*, 2*S*, 3*S*) prephytoene alcohols have been chemically synthesized and only the (1*R*, 2*R*, 3*R*) enantiomer (**91**), as the pyrophosphate ester, is biologically active[120, 169]. The absolute configuration of prephytoene pyrophosphate (**89**) is thus identical to that found for presqualene pyrophosphate (**77**)[138] and the detailed stereochemistry of the formation of these compounds is probably identical.



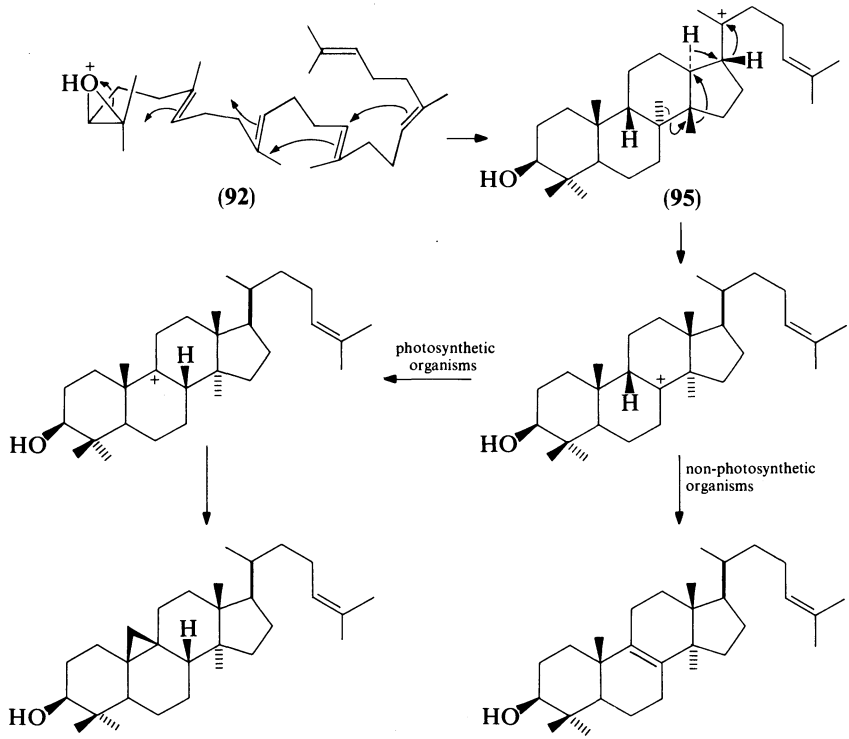
(1*R*, 2*R*, 3*R*) (**91**)

The studies on squalene (**76**) biosynthesis as the key acyclic precursor to natural steroids and on phytoene (**88**) as the central precursor to carotenoids and retinoids emphasize the enormously consequential role that the cyclopropyl group plays in the biological strategy for construction of thousands of natural compounds. For head-to-head reductive joining of two allylic alcohol pyrophosphates to generate C–C bonds either at sp^3–sp^3 or at sp^2–sp^2 oxidation states, formation and reactions of the cyclopropylcarbinyl group appears to be the common and only mechanistic route available to the enzymic inventory of organisms, whether bacteria, plants, or animals. A more thorough understanding of the

mechanistic and energetic features of these crucial carbon–carbon bond formation and rearrangement processes await the ready availability of pure, active squalene synthetase and phytoene synthetase in quantity.

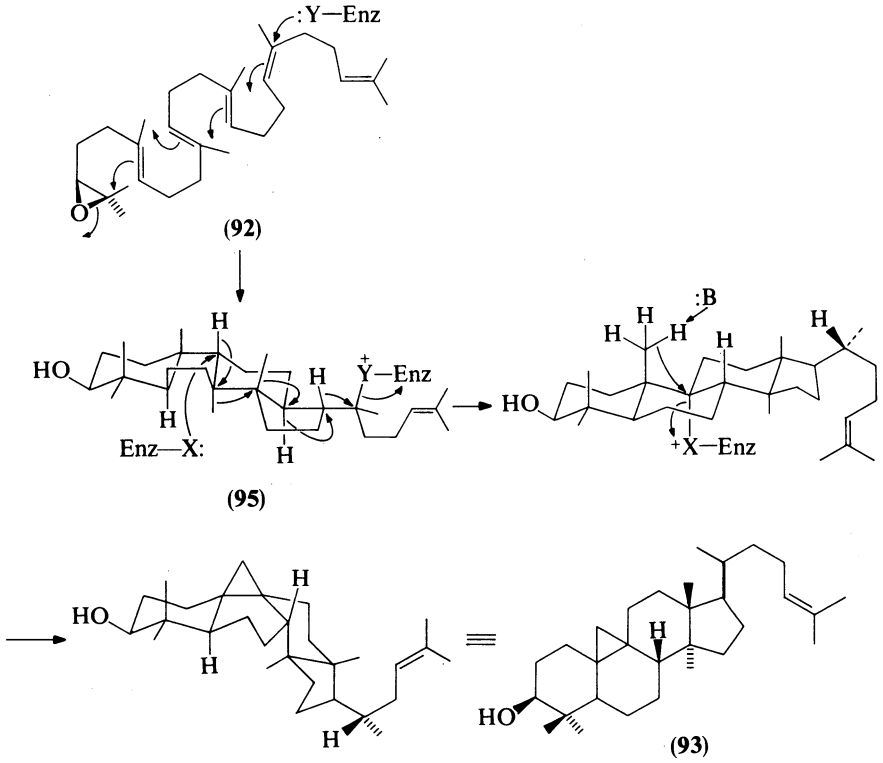
B. Cyclopropane Formation in Steroids by Participation of the Angular Methyl Group: Squalene to Cycloartenol

The biosynthesis of triterpenes by photosynthetic organisms proceeds via cyclization of 2,3-oxidosqualene (**92**) to yield cycloartenol (**93**), in contrast to non-photosynthetic organisms where the cyclization product is lanosterol (**94**)[170, 171]. The last step in this



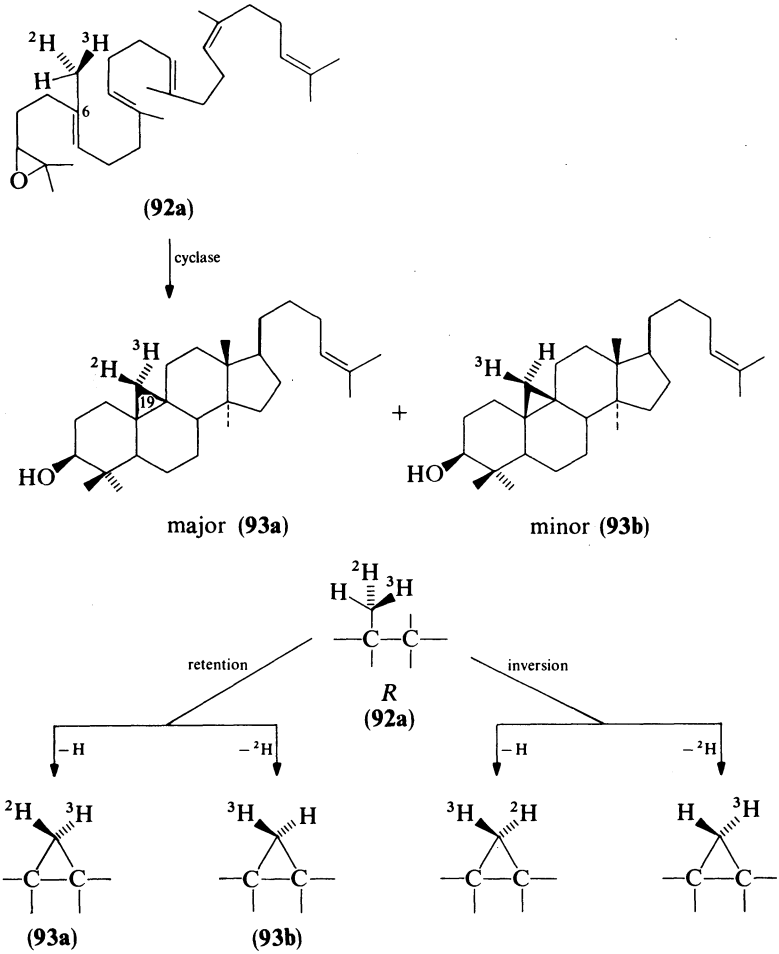
biosynthetic pathway leading to cycloartenol (**93**) involves proton loss from an angular methyl group to form the cyclopropane ring. Formation of this cyclic sterol precursor is mediated by 2,3-oxidosqualene: cycloartenol cyclase (EC5.4.99.8). This enzyme has been purified 25-fold from microsomes of *Ochromonas malhamensis*[172]. It has also been found in microsomes from tissue cultures of tobacco[173] and bramble[174], in barely coleoptiles, and in cell-free extracts of bean leaves of *Phaseolus vulgaris*[175].

The proposed reaction sequence to generate cycloartenol (**93**) includes squalene 2,3-epoxide (**92**) cyclization, active-site nucleophile assisted angular methyl and hydrogen group migration in the initial formed protosterol intermediate (**95**), and proton abstraction from the methyl group coupled to Enz-X group expulsion to form the three-membered ring (equation 17)[176]. It is as yet uncertain whether the cyclization leads to a



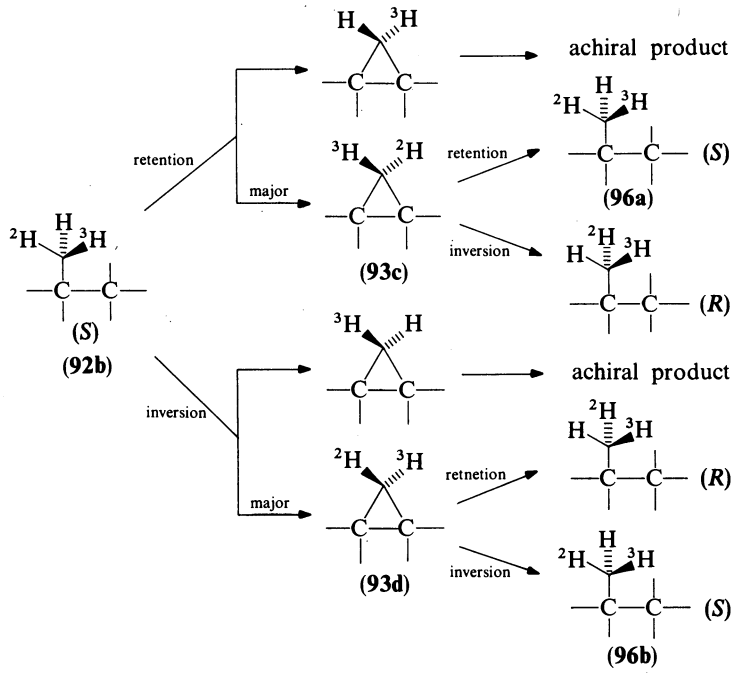
(17)

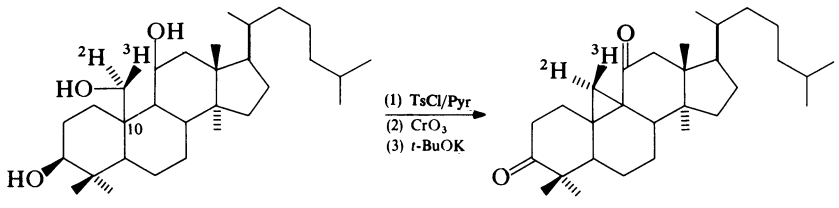
free protosterol carbocation (**95**) from which 1,2-shifts occur, or whether cyclization is initiated by nucleophilic attack of an enzymatic nucleophile, shown as Enz-Y in equation 17, at the terminus of the polyene system (**92**). How concerted the ring cyclization and/or the 1,2-migrations may be is also unknown. The involvement of an active-site nucleophile, Enz-X, at C(9) from below has been postulated since direct formation of cycloartenol (**93**) from squalene epoxide (**92**) with a chair–boat–chair conformation would require the migration of a hydrogen from the C(10) methyl group (*cis* to the C(9) hydrogen) to C(9), a process that is biogenetically unfavored[177]. The participation of that enzymatic nucleophilic group would allow the ensuing adduct to have the right geometry suitable for 1,3-*trans* elimination of the proton from the C(10) methyl group and the initially added Enz-X nucleophile (shown in equation 17). The stereochemical outcome of this enzymatic reaction, starting from squalene-2,3-epoxide carrying a chiral methyl group of predominately (*R*) absolute configuration at C(6), has been examined by Altman and coworkers with a microsomal preparation from *Ochromonas malhamensis*[178]. ^{3}H-NMR analysis of the resulting tritium-labeled products showed that the major species (**93a**) contained exo-tritium (Pro-*R*) and endo-deuterium (Pro-*S*) around the C(19) methylene group. This indicates that the conversion has proceeded with retention of configuration. The same conclusion was also derived independently by Arigoni and Blattler[179] from experiments using stereospecifically labeled squalene epoxide (**92b**) and cyclase obtained from maize. The cycloartenol product was subjected to hydrogenation to saturate the side

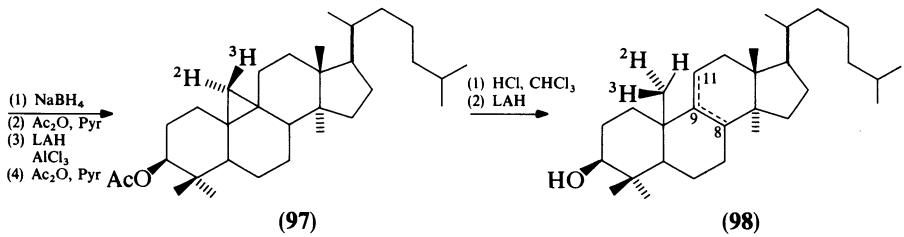


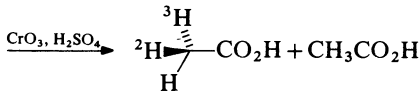
chain double bond followed by acid treatment to open the cyclopropane ring. The C(10) methyl group isolated as acetate from Kuhn–Roth degradation was shown to have the same chirality as the methyl group at C(6) in the squalene-2,3-epoxide used as substrate (**92b**). Thus, enzymatic ring formation as well as chemical ring fragmentation must have occurred via the same steric course (either **92b** → **93c** → **96a** or **92b** → **93d** → **96b**). Cycloartanyl acetate (**97**) samples having tritium and deuterium stereospecifically labeled at C(19) were then chemically synthesized and subjected to acid-catalyzed ring-opening reaction (equation 18). Chirality analysis of the acetates obtained from Kuhn–Roth oxidation of the resulting products (**98**) (having double bond at either C(8, 9) or C(9, 11) position) clearly indicated that the chemical ring-opening process proceeds cleanly with retention[179]. Therefore, the enzymatic ring-closure must also proceed with retention of configuration.

How the cycloartenol cyclase abstracts an unactivated C(10) methyl hydrogen as a proton in a low energy transition state to assist Enz-X loss and generate the cyclopropyl group is not known.


retention
major
inversion
(S)
(92b)
(93c)
(93d)
achiral product
retention
inversion
(96a)
(96b)
(S)
(R)
retnetion


(1) TsCl/Pyr
(2) CrO3
(3) t-BuOK

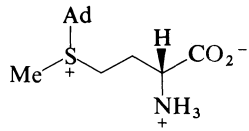

(1) NaBH4
(2) Ac2O, Pyr
(3) LAH
AlCl3
(4) Ac2O, Pyr
(1) HCl, CHCl3
(2) LAH
(97)
(98)


CrO3, H2SO4
CO2H + CH3CO2H

(18)

C. Cyclopropyl Group Formation via Addition of a One-carbon Fragment from *S*-Adenosylmethionine

S-Adenosylmethionine (SAM) (**99**) with its cationic sulfonium group is activated for methyl transfer, for adenosyl transfer, and for α-aminobutyryl transfer to some

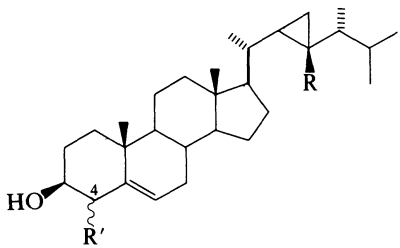


Ad: Adenosyl (**99**)

cosubstrate nucleophile. All three electrophilic group transfers are known in biological systems but the methyl transfer reactions are by far the most common and SAM is the major biological methylation reagent. Enzymatic transfer of the activated one-carbon unit of SAM to olefins has two outcomes, construction of a methyl branch (e.g. in 10-methyl stearate biogenesis from the Δ^9-olefin oleate) or construction of a cyclopropane group. The first two examples in this section deal with such cyclopropanations. The third example also uses SAM but involves a remarkable and economical internal cyclization of the activated methionyl side chain of SAM to 1-aminocyclopropane-1-carboxylic acid (ACPC) (**9**).

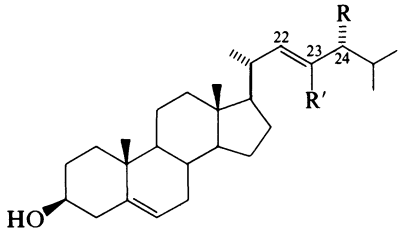
1. Biosynthesis of steroids with cyclopropane or cyclopropene-containing side chain

Gorgosterol (**17**)[40, 180] and its naturally occurring relatives, 23-demethylgorgosterol (**100**)[181] and 4-methylgorgosterol (**101**)[182], have all been isolated from marine sources. The occurrence of these unconventional sterols in nature presents an intriguing biosynthetic problem and also suggests that novel steps might take place in the functionalization of the sterol side chains. Until 1970, alkylation had only been found at C(24) (not at C(22) and C(23)), and the possible formation of intermediate cyclopropane rings was only postulated in the bioalkylation of the sterol side chain[183]. Based on the

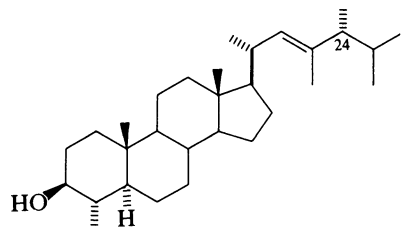


R = Me R′ = H gorgosterol (**17**)
R = R′ = H 23-demethylgorgosterol (**100**)
R = R′ = Me 4-methylgorgosterol (**101**)

stereostructure of gorgosterol (**17**), Djerassi and his coworkers had suggested[180] that brassicasterol (**102**) which possesses the same C(24)(*R*) stereochemistry and frequently coexists with gorgosterol (**17**) may serve as the key precursor of gorgosterol (**17**). The isolation of 23,24-dimethyl-22-dehydrocholesterol with gorgosterol and 23-demethylgorgosterol in a variety of coelenterates[184], the presence of 23,24-dimethyl-23-dehydrocholesterol in soft coral of *Sarcophyta elegans*[185] and the natural occurrence of



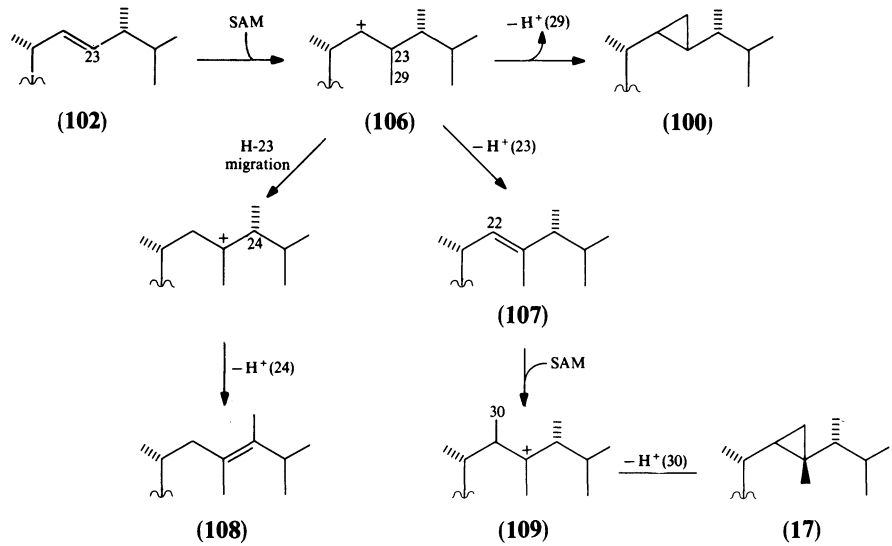
R = Me R′ = H brassicasterol (**102**)
R = R′ = Me (24ξ) (**103**)
R = R′ = Me (Δ^{23}) (**104**)



dinosterol (**105**)

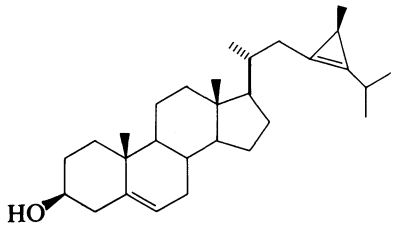
dinosterol (**105**) in dinoflagellate, *Gonyaulax tamarensis*[186] seem to support this proposed scheme, since they all possess the same side chain substitution patterns. These also afford indirect evidence that the gorgosterol methylation sequence might occur in the order C(24) → C(23) → C(22). However, the structure of 24-demethyldinosterol, the first C(23) side chain monoalkylated sterol isolated from the dinoflagellate *Gonyaulax diagenesis*[187], implies that a different order of methylation may be possible.

Similar to the cases encountered in the biosynthesis of cyclopropane-containing fatty acids and phytosterols[178, 183, 188], conventional alkylation of brassicasterol (**102**) with *S*-adenosylmethionine (**99**) at C(23) followed by the loss of a proton from the just introduced C(29) methyl group would afford the cyclopropane of 23-demethylgorgosterol (**100**) directly[189]. The intermediacy of the key carbocation (**106**) is supported by the natural occurrence of **107**[184], which may very likely be generated from **106** by simple proton abstraction from C(23). Further support of the intermediacy of **106** derived from the idea

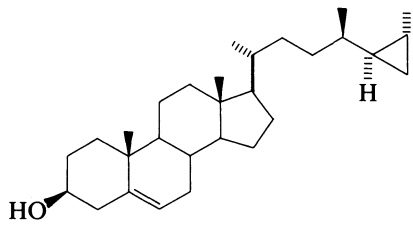


that a proton migration from C(23) to C(22) followed by C(24) proton ejection would lead to **108** which has also been found in nature[185]. A second alkylation of the C(22, 23) double bond of **107**, via the carbocation **109** and C(30) proton ejection to form the cyclopropane, would then produce gorgosterol (**17**).

Other biogenetically distinct cyclopropane side chain substitution patterns are typified by the sponge sterols calysterol (**25**) isolated from *Calyx nicaensis*[190], and petrosterol (**19**) found in *Petrosia ficiformis*[191–193] . Unlike the biosynthesis of gorgosterol-type (**17**)

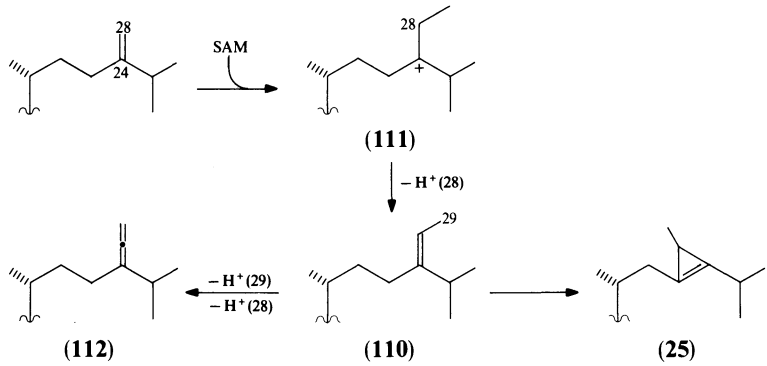


calysterol (**25**)



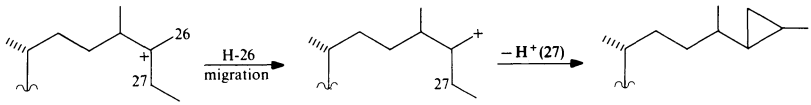
petrosterol (**19**)

cyclopropanes, incorporation of acetate and methionine in calysterol (**25**) is very low[194], and fucosterol (**110**) appears to be a good substrate for the synthesis of these unusual cyclopropane and cyclopropene side chain. Thus, formation of calysterol (**25**), and possibly petrosterol (**19**) as well, may rely on the contribution of dietary sources, with the sponge and its symbionts performing modifications on the exogeneous sterols.



A possible sequence proposed by Djerassi and his coworkers[189] starts with the carbocation intermediate (**111**) which is believed to be the initial product from methyl transfer from *S*-adenosylmethionine (**99**) to 24-methylenecholesterol. This intermediate, upon loss of a C(28) proton, would generate fucosterol (**110**). Since fucosterol (**110**) has been shown to be the precursor of calysterol (**25**), migration of the double bond of fucosterol (**110**) followed by dehydrogenation would then directly produce the cyclopropene moiety (**25**). The recent isolation of an unusual isofucosteroidal allene, 24-ethyl-$\Delta^{5,24(28),28}$ -cholestatrien-3β-ol (**112**) from the sponge *Callyspongia diffusa*[195] further supports the possibility that fucosterol (**110**) may undergo a formal dehydrogenation via cyclization to the cyclopropene.

By analogy to the postulated biosynthesis of calysterol (**25**) via carbocation (**111**) a similar sequence from the related carbocation intermediate (**113**) would yield the cyclopropane in petrosterol (**19**) directly.

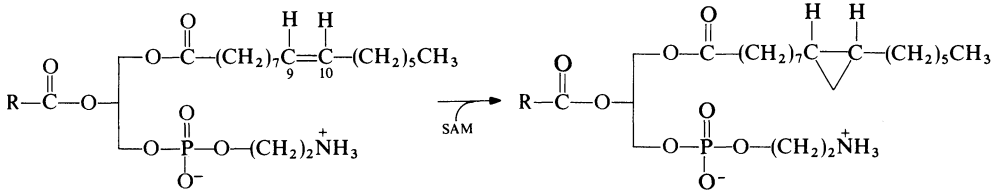


(113) (19)

2. *Biosynthesis of cyclopropane-containing fatty acids*

Fatty acids containing cyclopropanes are relatively common constituents of bacterial and plant lipids[196] where the precursors are obviously the corresponding olefinic fatty acids[197]. Common olefinic loci are Δ^9 in C_{16} and Δ^{11} in C_{18} fatty acids and the subsequent cyclopropanation products have corresponding 9, 10 or 11, 12 cyclopropane groups.

The most detailed study has been carried out with a 50-fold purified enzyme preparation from *Clostridium butylicium*[198] where the substrate is not the free olefinic fatty acid but a corresponding diacyl phospholipid (**114**). The enzyme displayed head group specificity for phosphatidylethanolamine and positional isomer preference of cyclopropanation for the acyl chain at C(1) of these glycerol-based phospholipids. For the monoolefinic C_{16} acyl chains, the Δ^9 olefin (**114**) was a much better cyclopropanation substrate than the Δ^7 olefins (even though the ratios of Δ^7/Δ^9 hexadecenoates in these populations is 2/1) while for the C_{18} monoolefins, the Δ^{11}-olefinic site was preferred kinetically 3:1 over the Δ^9-olefinic sites[199].



(114)

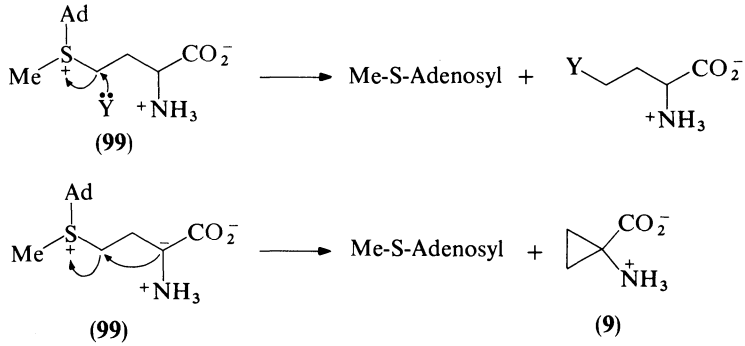
The mechanism of cyclopropanation itself has not been studied. In the possibly analogous biosynthesis of 10-methylstearate from oleate and SAM (**99**), a 10-methylene intermediate is produced with net 1,2-hydride migration. Then the 10-methylene is reduced to the 10-methyl product. In the cyclopropane case, 9,10-D_2-olefinic substrate showed no deuteride migration suggesting against an analogous intermediacy of a discrete 10-methylene isomer[197]. It is reasonable to suggest a methyl branched carbocation at C(9) or C(10) with subsequent proton abstraction from the methyl group and collapse to the 9,10-cyclopropane.

The accumulation of cyclopropane fatty acid-containing phospholipids is promoted in bacteria by low pH and low pO_2, conditions which attend entrance into stationary phase cultures. The conversion of olefin to cyclopropane alters membrane fluidity and probably other functional parameters as well and may be a physiological response to altered environmental conditions.

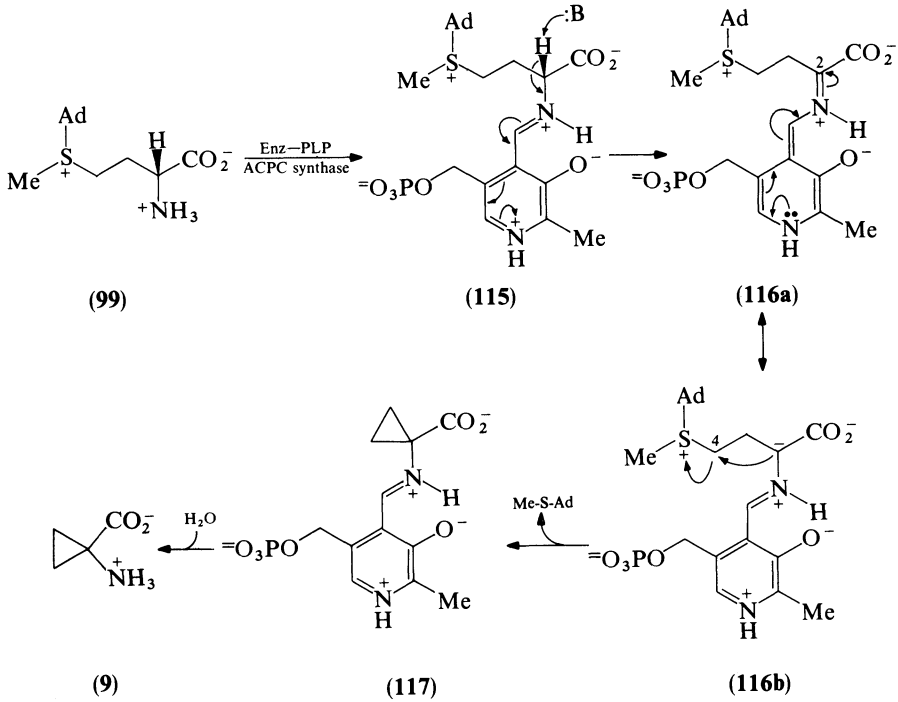
3. *Biogenesis of 1-aminocyclopropane-1-carboxylic acid (ACPC)*

The simple cyclopropanoid amino acid ACPC (**9**) is a constituent of many fruits and plant tissues where it serves as the immediate precursor of the plant hormone ethylene (**139**)[19–21]. That O_2-dependent fragmentation is covered in Section III of this chapter. Biosynthesis of ACPC (**9**) is the issue here. It has long been known that the ethylene

carbons derive from C(3) and C(4) of the key α-amino acid methionine, and the detection of ACPC as the kinetically and chemically competent intermediate by Adams and Yang[200] in 1979 was a key contribution. Yang and coworkers further showed that methionine was converted to *S*-adenosylmethionine (SAM) (**99**) and this served, with a partially purified enzyme from tomato[201,202]. ACPC synthase, as the direct precursor to ACPC (**9**). This enzyme appears to use pyridoxal-5′-phosphate (PLP) as a coenzyme and this last fact permits a rational description of this unusual cyclopropanation as an *anion-initiated event*, in contrast to many of the cation-initiated cyclopropane closures noted in the preceding cases.



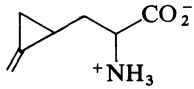
The sulfonium group in SAM (**99**) of course not only activates the methyl group for nucleophilic attack (the major biological role of SAM (**99**) the carrier of one carbon



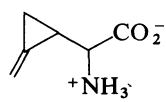
fragment at the methyl oxidation state) but also activates the other two substituents, adenosyl and methionyl, for cognate carbon–sulphur cleavages so C(4) of the α-aminobutyryl group is activated for nucleophilic displacement[203]. In this case the nucleophile is not external, on some cosubstrate, but is internal at C(2) of the methionyl arm. The C(2) carbanion equivalent is thermodynamically and kinetically accessible via the PLP coenzyme in the ACPC synthase active site. Imine (**115**) formation between substrate SAM (**99**) and PLP leads to facile C(2)–H cleavage to the stabilized C(2) anion (**116a** and **116b**) which is used as the internal nucleophile to attack C(4) and eliminate 5-thiomethyladenosine. Hydrolysis of the resultant PLP–ACPC aldimine complex (**117**) completes the reaction. The stereochemical outcome at C(4) is inversion as one would anticipate[204] for such a mechanism. This elegantly economical generation of the cyclopropyl amino acid may also be the route for the biosynthesis of the 2-ethyl ACPC (**8**) part of coronamic acid[16], but may not be the route for the guanidino ethyl ACPC[205] where the olefinic amino acid would also be a viable precursor for cyclopropanation and for which there is yet no information. At present, then, ACPC (**9**) biogenesis is the only well documented case of biological cyclopropane construction by *anion-initiated cyclization.*

4. Biosynthesis of hypoglycine A

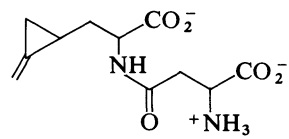
Hypoglycine A (**7**), a hypoglycemic compound, was first isolated from the akee plant *Blighia sapida* Kon.[13–15]. This amino acid, together with α-(methylenecyclopropyl)glycine



(**7**)

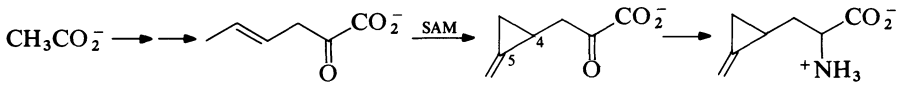


(**118**)



(**119**)

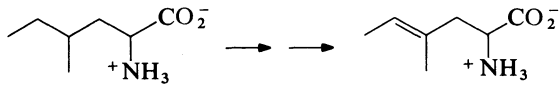
(**118**) and their derived γ-glutamyl peptides (**119**), had also been found as constituents in several related plant families, Sapindaceae, Hippocastanaceae, and Aceraceae[206–209]. The ability of several ^{14}C-labeled compounds to act as precursors of carbon atoms of the hypoglycine A (**7**) skeleton were examined during the phase of rapid growth of sycamore seeds, *Acer pseudoplatanis*[210]. In this study, only slight incorporation of label from [^{14}C]isoleucine (0.02%) was found in hypoglycine A (**7**). Higher, though still low, incorporation percentages were found with methyl-[^{14}C]-methionine (0.118%) and [^{14}C]acetate (0.051%). No incorporation of radioactivity from ^{14}C-labeled leucine was detected. These results suggested that biosynthetic formation of hypoglycine A (**7**) may



(**120**) (**7**) (19)

proceed by condensation of three acetate units to give a C_6-skeleton (**120**), followed by formation of the cyclopropane ring by formal addition of the methyl group of methionine at a position of 4,5-unsaturation (of **120**; equation 19) in analogy to the cyclopropyl fatty acids discussed earlier. Similar data were obtained in the biosynthetic study of hypoglycine A (**7**) in developing fruit of *Blighia sapida* where acetate and the methyl group from methionine again represent the most effective precursors of the carbon skeleton of

hypoglycine A (7) [211]. However, this proposed pathway is quite different from that of 2-amino-4-methylhex-4-enoic acid (**121**) found in related plants. Biosynthesis studies of the latter amino acid clearly indicated that isoleucine (**122**) was incorporated about ten times more efficiently than any other ^{14}C-labeled precursor tested[211].

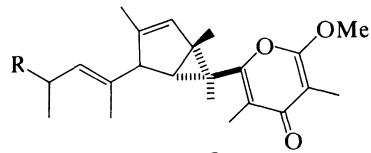


(**122**) (**121**)

Nothing is known about the biological conversion of the proposed methylcyclopropane species to the methylene cyclopropyl group found in the hypoglycine (**7**) skeleton. This can be effected chemically by phenylselenoxide elimination from the cyclopropylcarbinol but this is unlikely to be directly analogous to the biosynthetic route.

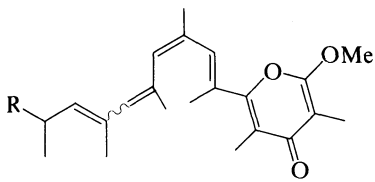
D. Photo-induced Cyclopropane Formation

Crispatene (**2**) and erispatene (**3**) have been isolated from *Tridachia crispata*[2]. This unique group of mollusks assimilate photosynthetically viable chloroplasts from siphonous algae upon which they graze. Biosynthesis of this type of compound could be



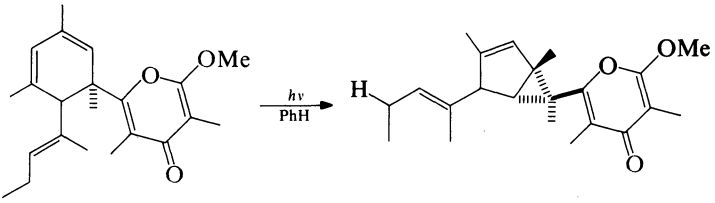
R = $MeCH_2C(=O)$—(**2**)
R = H (**3**)

envisioned from eight propionate units via either abnormal condensation routes or by molecular rearrangement. However, a more appealing pathway is based on a photochemical cyclization mechanism in which a molecule of a (6*E*,8*Z*,10*Z*)-hexatriene (**123**)



(**123**)

could be the precursor of crispatene (**2**) and its analogues. This is an attractive hypothesis since this reaction takes place in the organisms that are known for their photosynthetic abilities. This hypothesis was substantiated by *in vitro* photolysis of a solution of 9,10-deoxytridachione (**124**) in benzene to obtain a single photoproduct (**125**) in 85% yield[2]. The retention of optical activity during photolysis and the absence of other products favors a $[{}_{\sigma}2_a + {}_{\sigma}2_a]$ mechanism[212]. It was later found that a related sacoglossan



9,10-deoxytridachione (**124**) (**125**)

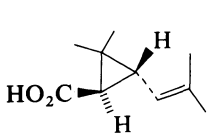
Placobranchus ocellatus contains both 9,10-deoxytridachione (**124**) and the photoproduct (**125**). This finding provides evidence supporting the relevance of a photochemical rearrangement *in vivo*[213].

III. BIOLOGICAL DEGRADATION OF CYCLOPROPANE RINGS

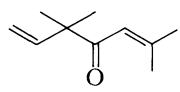
In this section we analyze information about metabolic cleavage or breakdown of cyclopropane rings in three instances: the biosynthesis of irregular monoterpenes, the ring-opening of cycloartenol (**20**) derivatives, and the metabolic opening of 1-aminocyclopropane-1-carboxylic acid (ACPC) (**9**) by two quite distinct fragmentation routes. We will not explicitly discuss the processing of presqualene pyrophosphate (**77**) and prephytoene pyrophosphate (**89**) to squalene (**76**) and phytoene (**88**) respectively, since those transformations have already been dealt with in Section II.

A. Degradation of Cyclopropane Rings in the Biosynthesis of Irregular Monoterpenes

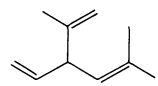
Chrysanthemic acid (**126**), artemesia ketone (**127**), santolina triene (**128**) and lavandulol (**129**) are representatives of irregular monoterpenes which, unlike other regular monoterpenes, are not derived directly from geranyl pyrophosphate (**59**). By contrast to the regular



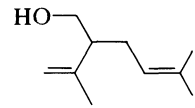
chrysanthemic acid (**126**)



artemesia ketone (**127**)

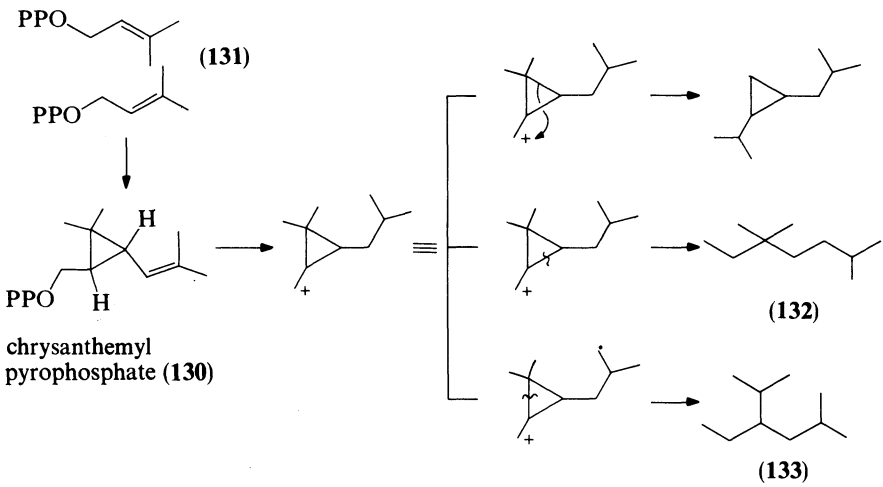


santolina triene (**128**)



lavandulol (**129**)

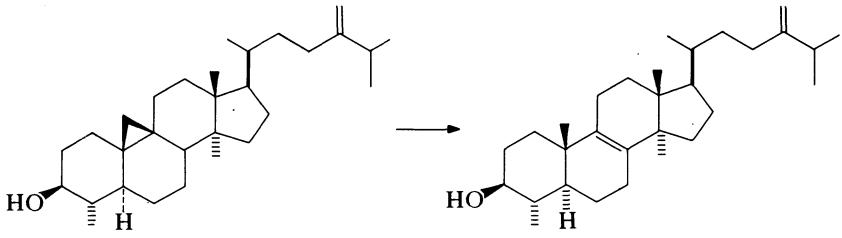
monoterpenes, only one enantiomer for chrysanthemic acid (**126**) type irregular compounds has thus far been reported and all belong to the same (1*R*, 3*R*) series[214,215]. Although there has been little experimental verification of any conjectured biosynthetic pathway, a unified hypothesis has been proposed based on the available data coupled with biosynthetic analogies to presqualene alcohol and the known chemical interconversions of the chrysanthemyl carbon skeleton with other non-head-to-tail monoterpenes[216,217]. The key intermediate, chrysanthemyl pyrophosphate (**130**), in this integrated scheme is readily derived from the condensation of two 3,3-dimethylallyl pyrophosphate molecules (**131**) and is the C_{10} analog of presqualene (**77**) and prephytoene pyrophosphate (**89**) (see Section II.A.5 and 6). However, chrysanthemyl pyrophosphate (**130**) has never been found in nature and the proposed cleavages of this key intermediate to yield various rearranged



skeletons has not yet been observed in the tri- and tetraterpene series either. Nevertheless, numerous model studies have demonstrated the feasibility of the proposed cyclopropylcarbinyl cation cleavage and the rearrangement of the chrysanthemyl system to the artemisane (**132**) and santolinane (**133**) skeletons[218–222]. Detailed mechanistic and stereochemical features of these cyclopropyl carbinyl cation rearrangements have also been studied in a number of cases[128–130,132]. Banthorpe and his coworkers had found that extracts from *Artemisia annua* and *Santolina chamaecyparissus* could convert various five-carbon precursors into artemisia ketone (**127**), its corresponding alcohol, lavandulol (**129**) and *trans*-chrysanthemyl alcohol[223,224]. The same extracts could also interconvert chrysanthemyl derivatives and artemisane monoterpenes. However, acyclic 10-carbon units such as nerol and linalol, or their pyrophosphates, were not precursors of any of these compounds. These observations provided the first direct evidence that the artemisyl and chrysanthemyl skeletons are closely related biogenetically, and formation of these irregular skeletons does not involve the usual C(10) intermediate of monoterpene biosynthesis. Attempts to purify this enzyme system have thus far been futile and limit further insights.

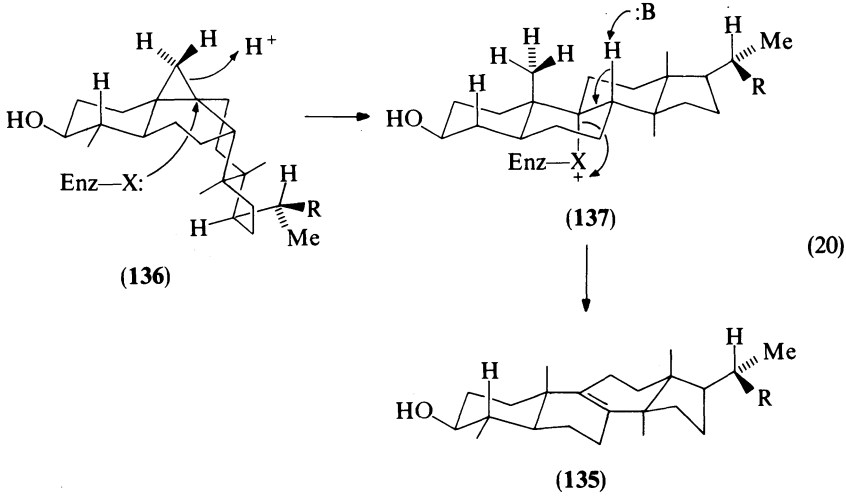
B. Ring-opening of Cycloartenol Derivatives

As mentioned in Section II, cycloartenol (**20**) is the first cyclic sterol precursor in the biosynthetic formation of sterols in higher plants and fungi[171]. The enzyme that opens the cyclopropane ring has been found in cell-free preparations from tissue cultures of bramble (*Rubus fruticosus*)[225]. Microsomes prepared from maize embryos[226,227], germinating peas and tobacco tissue cultures are also reported to have this enzyme activity. However, rabbit liver microsomes and yeast enzymes are inactive. This enzyme could convert cycloeucalenol (**134**) into obtusifoliol (**135**) without addition of ATP or NADH[226,227]. This enzymatic process has been proposed to proceed as shown in equation 20 with nucleophilic enzyme-X group attack at C(9) (of **136**), the ring junction, to open the cyclopropane ring and produce the angular methyl in the transient enzyme adduct (**137**) Subsequent antiperiplanar elimination of the 8β-hydrogen and the Enz-X group leads to



cycloeucalenol (**134**) obtusifoliol (**135**)

the formation of obtusifoliol (**135**)[225]. Consistent with the proposed mechanism, the incorporation of one solvent deuterium into **135** was observed when the reaction was



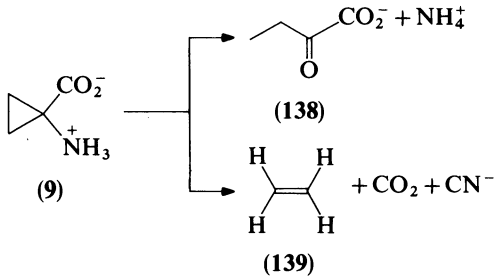
(**136**) (**137**) (**135**) (20)

conducted in deuterated solvent with Zea may (Gramineae) embryos and cycloeucalenol (**134**) as substrate[226,227]. With the same methodology as employed in the stereochemical analysis of cycloartenol (**20**) formation, studies of the stereochemical course of this ring cleavage reaction were carried out on synthetic stereospecifically labeled (19*S*)-[19-^{2}H, 19-^{3}H]-31-norcycloartenol with the enzyme from maize seedlings[179]. As observed for the cycloartenol (**20**) case, the acetates isolated from the Kuhn–Roth degradation of the ring-opening products derived either chemically (acid-catalyzed) or enzymatically, have the same chirality[179]. Thus, the chemical and enzymatic ring cleavage processes must proceed via the same steric course. Since the acid-catalyzed step has been shown to proceed with retention[179], these enzymatic ring-opening proceeds in a retention mode as well.

The enzyme prepared from bramble tissue cultures has been reported not to recognize cycloartenol (**20**) and 24-methylenecycloartenol as substrates[225]. Therefore, the C(4) demethylation presumably occurs prior to opening of the cyclopropane ring. The presence of a 4β-methyl group in cycloartenol (**20**) and 24-methylenecycloartenol might hinder cyclopropane ring-opening by the unfavorable 4β-methyl with 10-methyl interaction in the resulting product as suggested by Heintz and Benveniste[225], or might simply inhibit the effective binding of the substrate with the enzyme.

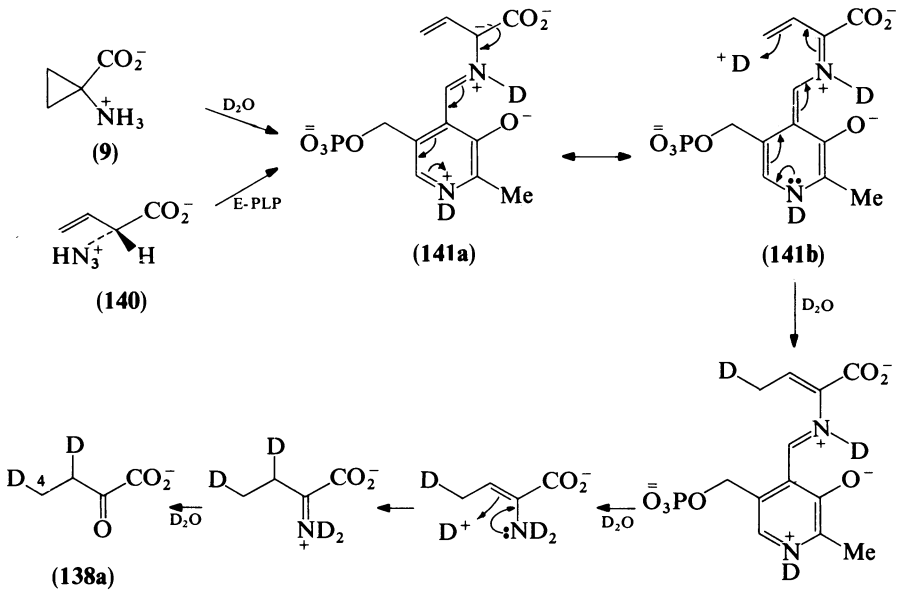
C. Enzymic Fragmentation of 1-Aminocyclopropane-1-carboxylic Acid (ACPC)

We noted earlier in this chapter (Section II.C.3) the pyridoxal-phosphate-linked enzymatic route of synthesis of ACPC (**9**) from the α-aminobutyryl moiety of *S*-adenosylmethionine (**99**). ACPC (**9**) undergoes further metabolic processing by two distinct fragmentation routes, to α-ketobutyrate (**138**) and ammonia (equation 21) in bacteria and yeast[228] or to ethylene (**139**) in fruit and other plant tissues (equation 22) where ethylene (**139**) is a potent hormone for fruit-ripening or wound-healing[21]. The bacterial enzyme, ACPC deaminase is much better characterized and is taken up first.



1. ACPC deaminase: ACPC to α-ketobutyrate

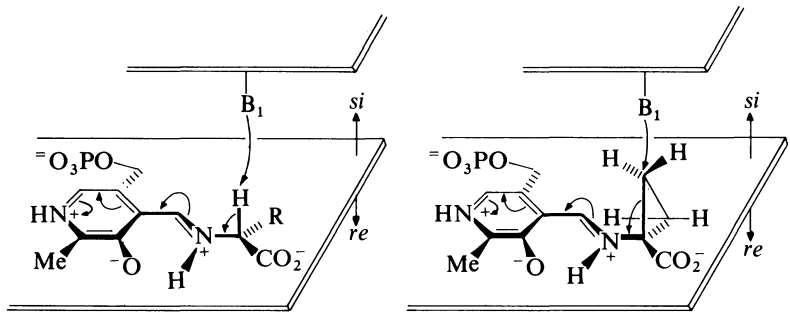
The deaminase has been purified by Honma and Shimomura[228] to homogeneity from *Pseudomonas* and has also been demonstrated to be a PLP-enzyme in some analogy to ACPC synthase. The K_m for ACPC (**9**) is 9.2 mM and the K_{cat} is 390 min^{-1}. The cleavage of ACPC (**9**) to α-ketobutyrate (**138**) is a novel one in PLP coenzyme biochemistry. The



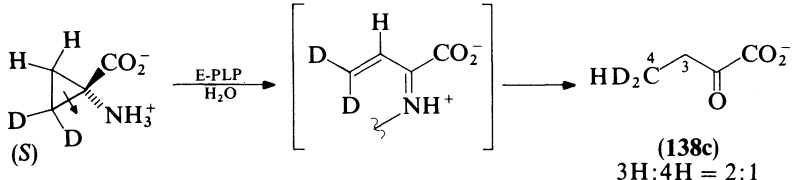
(23)

C(α)–C(β) bond cleavage in α-amino acids is precedented by the PLP-containing enzyme serine hydroxymethyltransferase, interconverting serine with glycine and a formaldehyde equivalent, but in that case C–C bond cleavage is a retro aldol process[229]. This route is not obviously open to ACPC (**9**).

When ACPC (**9**) is cleaved by deaminase in D_2O, one deuterium is incorporated at C(3) and one at C(4)[230]. Although ACPC (**9**) has no α-H, the enzyme will catalyze reversible exchange of the α-H in D-alanine but not in L-alanine. This led to the testing of D-vinylglycine (VG) (**140**) as substrate and the finding that it was smoothly converted to α-ketobutyrate (**138**) with the same deuterium incorporation pattern (C(3), C(4)) (in **138a**) in D_2O. It is therefore likely that the α-anion equivalent of the vinylglycyl-PLP aldimine (**141a** and **141b**) is a key intermediate in ACPC fragmentation as shown in equation 23. From the acyclic α-anion onward one can readily explain the deuterium incorporation at C(3) and C(4) of product. The fact that ACPC deaminase can process either a D-α-amino acid or the ACPC (**9**) suggests the following orientation of substrates in the active site of the deaminase enzyme.

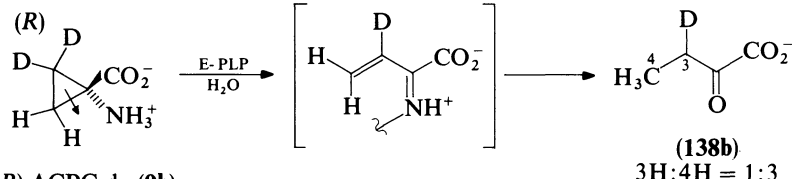


A detailed set of stereochemical studies have been conducted on the ACPC deaminase reaction. The regiochemistry of ACPC (**9**) C–C fragmentation was established to be exclusively between the α-C and the Pro-*S* β-CH_2 group by synthesis and incubation of *R*-(−)-[2,2-D_2]- (**9b**) and (*S*)-(+)-[2,2-D_2]-ACPC (**9a**), which yield [3-D_1]-(**138b**) and [4-D_2]-2-keto butyrate (**138c**) respectively[231]. Additional stereochemical studies[232] employ



(*S*)-ACPC-d_2 (**9a**)

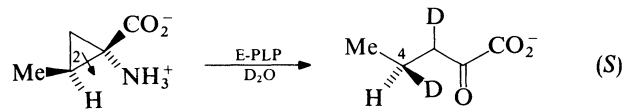
(**138c**)
3H:4H = 2:1



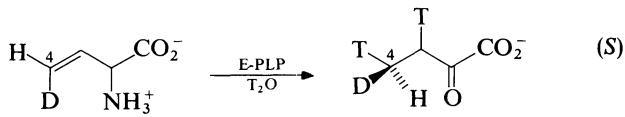
(*R*)-ACPC-d_2 (**9b**)

(**138b**)
3H:4H = 1:3

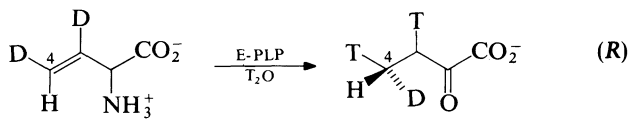
(*E*)-[3,4-D_2]- (**140a**) and (*Z*)-[4-D]-vinylglycine (**140b**) in T_2O to analyze the CHDT-group of the product 2-ketobutyrates (**138d** and **138e**) by chiral methyl group analysis and so deduce stereochemical outcome at C(4). As an independent assessment for stereochemical outcome, at C(4) in the 2-ketobutyrate product, (1*S*,2*S*)-2-methyl-ACPC (**142**) (the enzyme uses the 1*S*,2*S*-diastereomer) was incubated in D_2O and the product (**143**) was decarboxylated to 3-D_1-butyrate which was further derivatized to the naphthoyl ester. Its chirality was determined by CD analysis as compared to that of the authentic (3*R*) and (3*S*)-[3-D_1] butyrate naphthoyl esters[232].



2-Me-ACPC (**142**) (**143**)



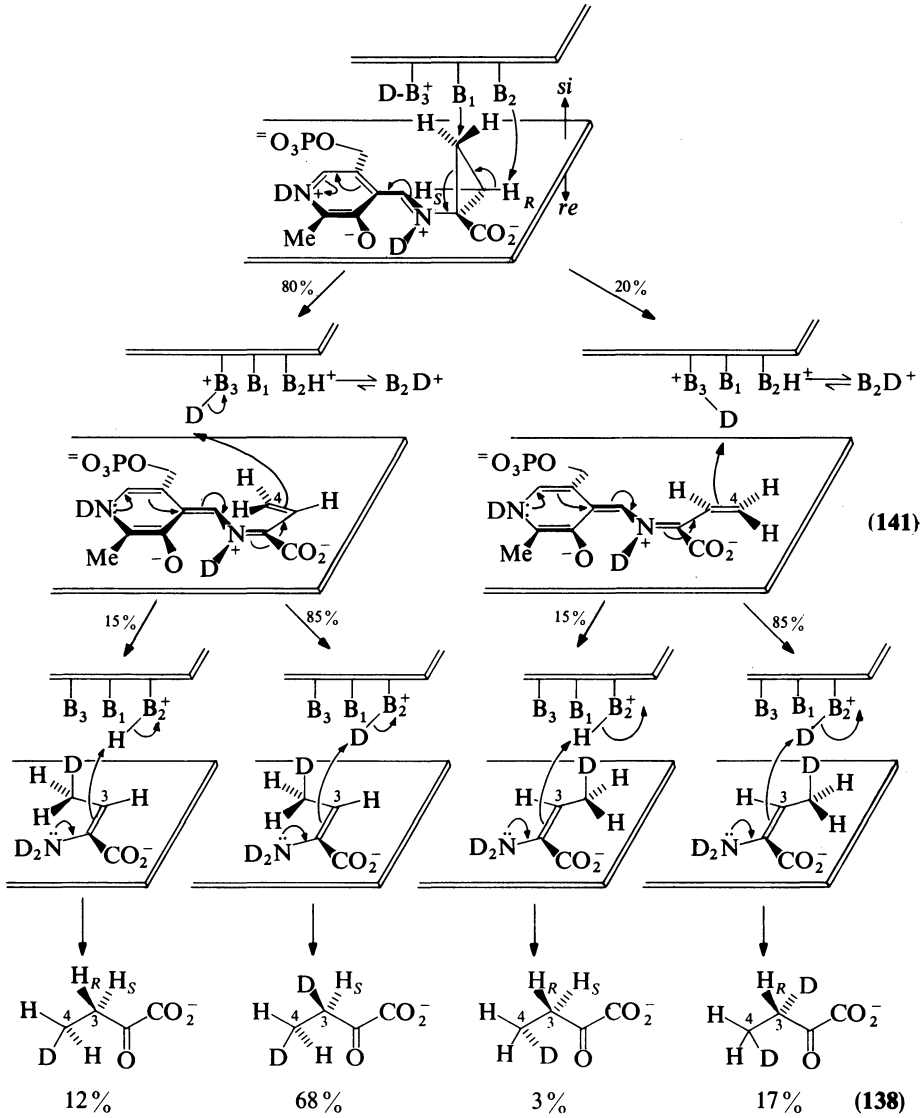
(*Z*)-4-D_1-VG (**140b**) (**138e**)



(*E*)-3,4-D_2-VG (**140a**) (**138d**)

To determine the stereoselectivity of diastereotopic proton abstraction from the Pro-*R* methylene group of ACPC (**9**) in the fragmentation (occurring between Pro-*S* β-C and α-C), 2-ethyl-[3-D_1]-ACPC (**8a**) was prepared with the ethyl side chain and deuterium substituent in *cis* relationship. Incubation of this compound followed by *in situ* reductive enzymatic trapping with (2*S*)-lactate dehydrogenase yielded 2-hydroxy-[3-D]-hexanoate where the *R*,*S*-placement of D was analyzed by NMR and the D-content by mass spectrometry. These results had defined the stereoselectivity for β-H-abstraction from the Pro-*R* methylene of 2-ethyl-ACPC (**8**) as the H_R proton removal in the overall fragmentation process and by analogy the same in ACPC (**9**). These results place stereochemical constraints on the ACPC deaminase process and were accommodated in Scheme 10.

First, the enzyme has at least two and probably three active-site basic groups involved in proton transfers to and from substrates, intermediates, and nascent products and all three bases are located on the *si* face of the substrate–PLP aldimine system as are the protons to be shuffled about, so all the proton transfers are likely to be economically suprafacial. Several pieces of stereochemical evidence[232] suggest that the β,γ-olefinic PLP-*p*-quinoidal-α-anion (**141**) can rotate around its C(β)–C(α) bond and also implicate that the cisoid isomer of this π complex and then the *Z*-isomer of the nascent aminocrotonate carry 80% of the reaction flux. Furthermore, a 15% internal retention of the H_R from the Pro-*R* methylene of ACPC (**9**) on B_2H^+ (85% exchange with solvent, 15% internal return) in the active site and the overall 22/78 : H_R/H_S distribution at C(3) of the mono- and dideutero 2-ketobutyrate (**138**) products at C(3) are also noted.

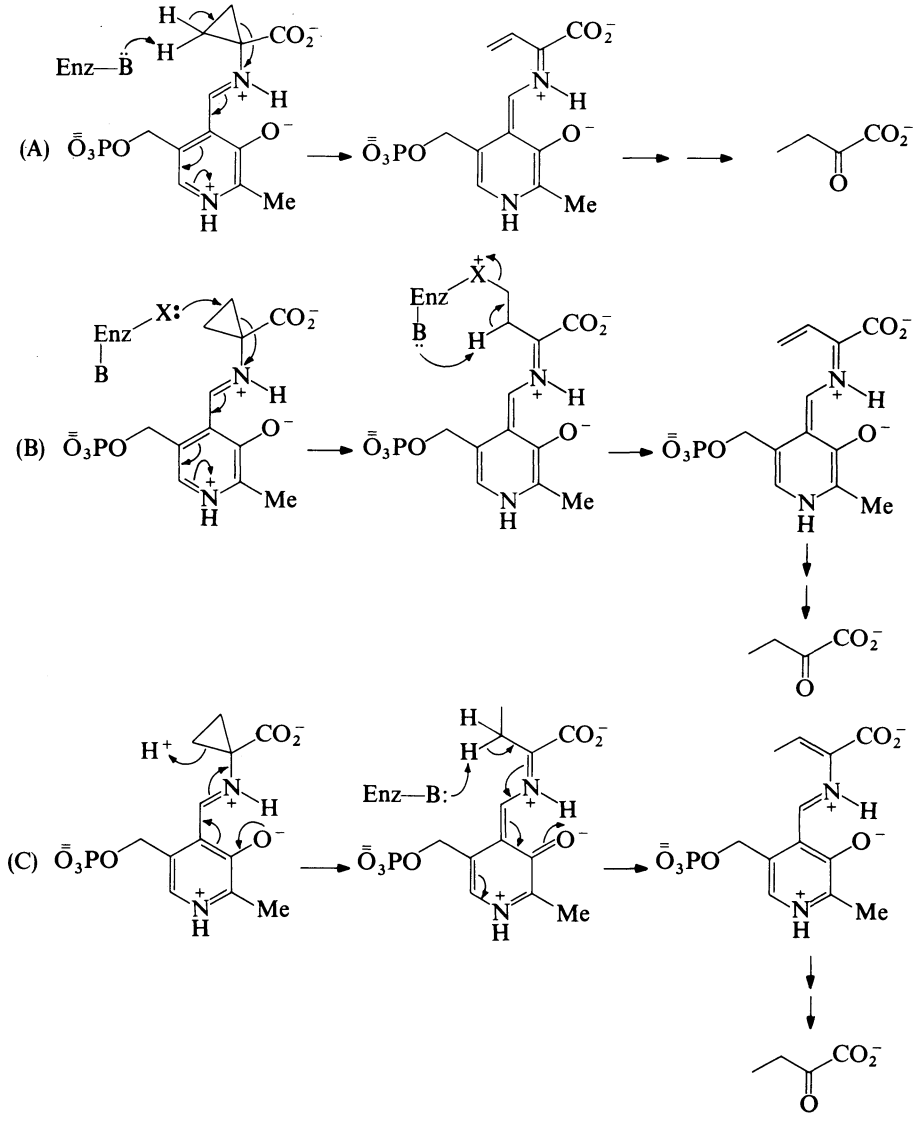


$H_R/H_S = 0.32H/0.83H = \boxed{22/78}$

$H_R + H_S = \boxed{1.15H}$

SCHEME 10

A major remaining issue in ACPC deaminase catalysis is the mode of actual cyclopropane fragmentation. At least three mechanistic variants can be pictured: (A) β-proton abstraction to initiate cyclopropane fragmentation; (B) nucleophilic addition to



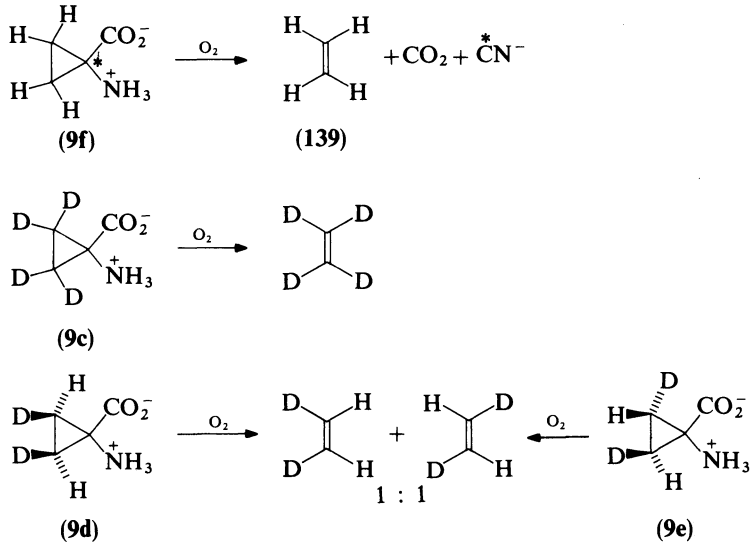
open the ring followed by β-proton abstraction; (C) protonation–fragmentation using the phenoxide oxygen of PLP as an electron donor. Mechanism (A) requires initiation of catalysis by abstraction of a proton from a rather inert C–H bond. Mechanism (B) invokes a unique covalent catalytic mechanism novel in PLP biochemistry but reasonably precedented in cyclopropane chemistry and has two virtues. First, the β-H abstracted, in the β-H, γ-X-enzyme elimination step to set up the key vinylglycyl-α-anion-PLP equivalent (**141**), is an acidic hydrogen in the ring-opened covalent enzyme–substrate adduct. Second, this process, considered in reverse, is essentially the mechanism for the PLP–enzyme ACPC synthase (Section II.C.3) and that seems to be a highly relevant precedent. The third

route is novel in proposing PLP not as the usual electron sink but as an electron donor. The push–pull proton-assisted cyclopropane fragmentation is precedented by model studies of Jencks[233] on phenylcyclopropane cleavage. No distinguishing experiments for these mechanistic alternatives are yet reported.

2. *ACPC fragmentation to ethylene*

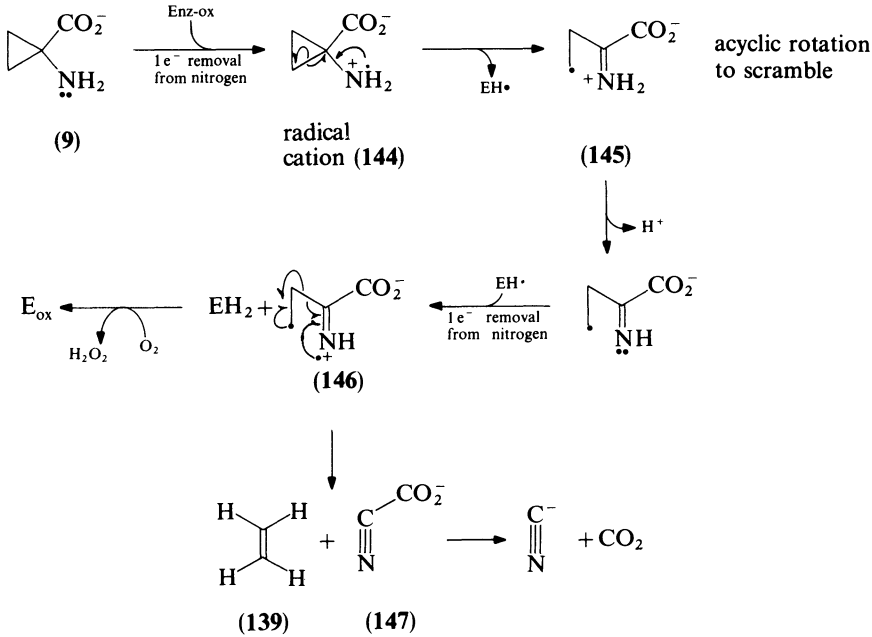
The fragmentation of ACPC (**9**) that leads to ethylene (**139**) is at least as remarkable, occurs in a much less well-characterized system (plant mitochondria) that has resisted purification, and has been mechanistically unobvious.

Nonetheless, dramatic advances have been made in the last three years by use of labeled substrates in crude tissue conversions. Baldwin and colleagues using apple slices[234] and Pirrung[235] and our group[236] using mungbean seedlings had observed that D_4-ACPC (**9c**) yields D_4-ethylene, thus no C–H cleavages appear to be involved in the cyclopropane fragmentation. With both *cis*-[2,3-D_2] (**9d**) and *trans*-[2,3-D_2]-ACPC (**9e**) the Oxford group[237] saw a 1:1 distribution of *cis*- and *trans*-[1,2-D_2]-ethylene, indicative of a complete stereochemical scrambling even though no C–H bonds suffer net cleavage (one could imagine C–H cleavage with fully sequestered protons but that goes against Occam's



razor). They suggested a cyclopropyl intermediate but posed no mechanistic solution to the stereochemical outcome[237]. Pirrung[238,239] has recently reported electrochemical model oxidations where C(1) of ACPC (**9**) (the carbon bearing amino and carboxylate groups) is converted to cyanide ion and he postulated one-electron oxidations by radical cation intermediates. Meanwhile we in collaboration with S. F. Yang's group in the Department of Vegetable Crops at U.C. Davis had shown that [1-^{14}C]-ACPC (**9f**) is converted to ^{14}C-cyanide ion which is then taken up and converted to [cyano-^{14}C]-β-cyanoalanine and ^{14}C-asparagine, this last metabolite solely labeled in the carboxamido carbon[240]. The convergence of model chemistry and enzymatic conversion in the crucial production of cyanide is both highly constraining and diagnostic of mechanism, and strongly supports the following version of the Pirrung proposal. This scheme proposes

one-electron removal from amino nitrogen to yield the amine radical (**144**) cation which induces opening of the cyclopropane to the carbon-centered primary radical and the imine (**145**). This high energy species must be very transient but could allow free rotation to account for the scrambled stereochemistry at the primary CH_2 site. A rapid removal of the second electron from the imine nitrogen yields another radical cation (**146**) which would



(**139**) (**147**)

collapse to yield ethylene (**139**) and cyanoformate (**147**), a species which would facilely decarboxylate to CN^- and CO_2. This accounts for (*a*) no loss of carbon-bound hydrogen in ACPC (**9**), (*b*) stereochemical scrambling, (*c*) conversion of carbon of ACPC (**9**) to sp-hybridized carbon in cyanide ion. Molecular oxygen is required for ACPC (**9**) conversion to ethylene (**139**) but neither stoichiometry nor product is known. While oxygenation schemes have been considered by others (e.g. *N*-oxygenation), we believe a flavoprotein amine oxidase mechanism is a likely precedent. The two one-electron steps could give enzyme-FADH, then enzyme-$FADH_2$ for example, and O_2 would be used merely to reoxidize enzyme and, in so doing, be reduced to H_2O_2.

IV. CYCLOPROPYL SUBSTRATES AND SUBSTRATE ANALOGS USES AS PROBES OF ENZYMATIC MECHANISMS

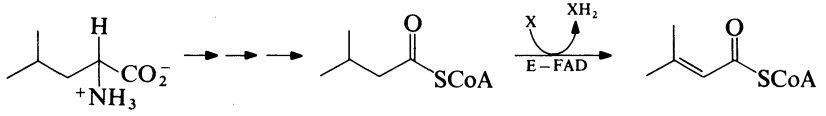
In the preceding sections we have noted the biosynthesis and/or catabolism of cyclopropyl moieties by carbocation, by carbanion and by radical processes in specific contexts. At least two naturally occurring cyclopropyl metabolites and several synthetic ones have been observed to induce inactivation of specific target enzymes. The inactivation is presumptively related to chemical reactivity of loci at or adjacent to the cyclopropane equivalent. In the case of hypoglycine A (**7**) the methylene cyclopropane group is the problematic moiety, while in coprine (**29**) the hemiaminal is a latent cyclopropanone equivalent; we shall analyze the proposed enzyme killing routes for each. Then we will turn to cyclopropyl

substrates which upon enzymatic oxidation leads to inactivation of specific enzymes. One-electron transfer to radical species during the oxidation of these cyclopropylcarbonyl or cyclopropylamino groups may unleash the autodestructive mode.

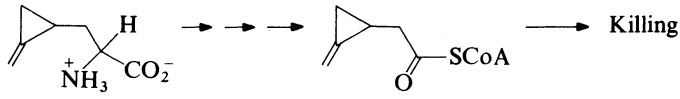
A. Naturally Occurring Cyclopropanoid Inactivators of Acyl CoA Dehydrogenase and Aldehyde Dehydrogenase

1. Hypoglycine A

As noted earlier the γ,δ-methylenecyclopropyl derivative of norvaline, hypoglycine A (**7**)[14,15], is the causative agent of Jamaican vomiting sickness. Hypoglycine A (**7**), ingested from unripe akee fruit, is processed by the normal branched chain amino acid degradative strategy for transamination, decarboxylation, and CoA thiolester formation in analogy to leucine (**148**), processing without untoward event to that point[241].



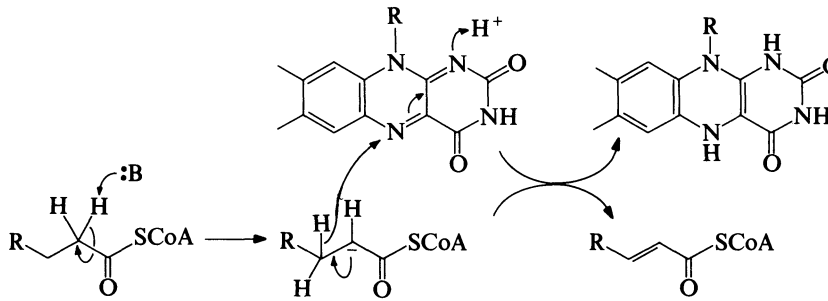
(**148**) (**149**) (**150**) (24)



(**7**) (**151**) (25)

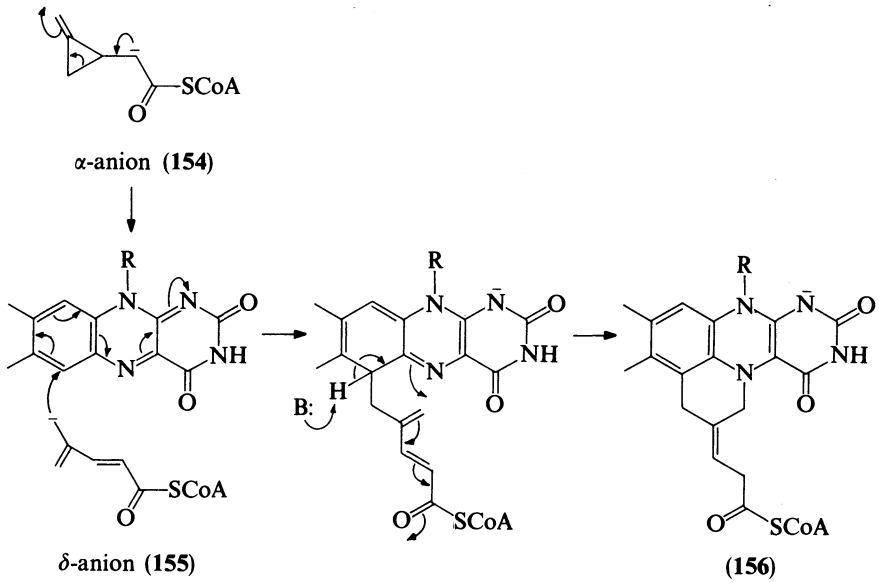
The normal branched chain isovaleryl CoA (**149**) is then desaturated to the α,β-enonyl CoA (**150**) by a flavin-linked branched chain acyl CoA dehydrogenase (equation 24). When the methylenecyclopropane acyl CoA (**151**) is exposed to acyl CoA dehydrogenase, time-dependent inactivation ensues with covalent modification of the bound FAD coenzyme (equation 25), possibly via a 6,5-adduct although the structure is unproven[242].

Mechanistic studies on acyl CoA desaturation by these FAD-dependent acyl CoA dehydrogenases strongly suggest proton–hydride redox pathways where one C(2) prochiral H (of **152**) is removed as a proton to give the stabilized α-anion (**153**) which



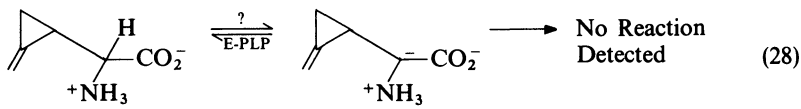
(**152**) (**153**) (26)

breaks down by C(3)–H expulsion as a hydride ion to N(5) of FAD to yield, in a net *trans* elimination, the α,β-enolyl CoA and E–$FADH_2$ (equation 26)[243]. When the methylene cyclopropyl acyl CoA (**151**) is presented at the active site for catalysis, formation of the C(2)-anion (**154**) is hypothesized[242] to perhaps lead to fragmentation of the adjacent methylenecyclopropyl group either by ε-protonation on the acyclic resonance hybrid or by use of that δ-anion (**155**) to covalently attack and modify the nearby FAD, putatively at



(27)

C(6) and then at N(5) (**156**) as shown in equation 27, based on optical changes of the flavin spectrum in the inactivated enzyme. The unwanted covalent modification of the bound FAD redox coenzyme is the cause of enzyme suicide. Whether this anionic rerouting of the methylenecyclopropyl analog of the normal reaction intermediate is the molecular basis of killing must await a full structure determination on the inactive flavoenzyme. To probe for possible generality of this proposal for adjacent-anion-induced fragmentation of methylenecyclopropanes, we[244] have tested the nor analog of hypoglycine A, methylenecyclopropylglycine (**157**) from lichee fruit, with PLP enzymes known to make stabilized α-anions, e.g. alanine racemases, but detected neither inactivation nor ring-opening (equation 28) so the general issue is still moot.

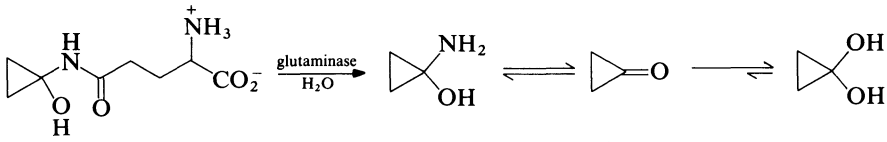


(157) (28)

2. Coprine

Coprine (**29**)[52] is an unusual γ-glutamylamide of cyclopropanone hydrate (**158**). The substituted hemiaminal (**29**) is stable in aqueous solutions but can be cleaved by hydrolytic

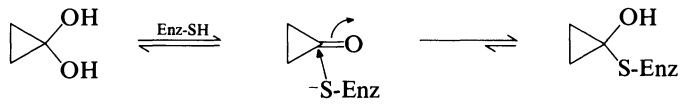
glutaminase enzymes in mammals (or in bacteria). Now the liberated cyclopropanone hemiaminal (**159**) is in rapidly established equilibrium with cyclopropanone (**160**). The



coprine (**29**) (**159**) + Glutamate (**160**) + NH_3 (**158**)

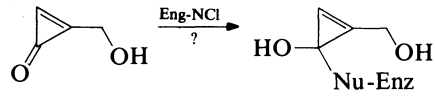
(29)

strained three-membered ring ketone (**160**) is a minor component in the equilibrium with the more stable hemiaminal (**159**) or hemiacetal (**158**) (equation 29). This tendency to accumulate as the stabilized tetrahedral adduct accounts for eventual toxicity of coprine (**29**) which, for example, can inactivate one of its metabolic targets, aldehyde dehydrogenase[245], known to have a kinetically reactive and essential cysteinyl thiolate side chain in its active site. The cyclopropanone hydrate (**158**) that enters this microenvironment rapidly accumulates as the covalent hemithioacetal–enzyme derivative (**161**) and thereby explains observed activity loss[246]. Other enzymes may also be similarly inactivated



(**158**) (**161**)

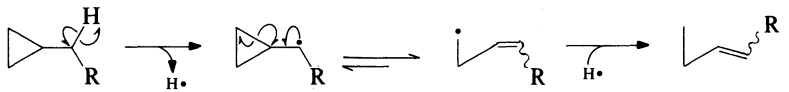
by cyclopropanone equivalents generated *in situ* by catalytic unraveling of some latent precursor. Finally, a cyclopropenone, penitricin (**26**)[49], recently discovered as a novel antibacterial could have similar molecular activity.



(**26**)

B. Radical Intermediates as Inactivators in Enzymatic Processing of Cyclopropylcarbinyl and Cyclopropylamino Substrates

The rearrangement of α-cyclopropyl radicals (**162**) to the ring-opened alkyl radical (**163**) has been recognized as an extremely rapid (ca. $10^8\ s^{-1}$) and useful radical clock reaction (equation 30)[247], with equilibrium greatly favoring the unstrained acyclic partner. In recent years this process has been used in enzymatic redox reactions to probe the nature of

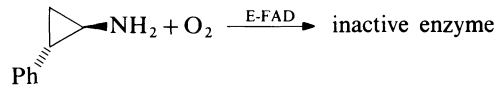


(**162**) (**163**) (30)

the electron transfer process, one-electron vs. two-electron (e.g. hydride) steps, and to generate autoinactivation of target enzymes. Three cases are illustrated below.

1. *Monoamine oxidase inactivation*

For some years the mitochondrial flavoenzyme monoamine oxidase (MAO) was the target of selective inhibition in the development of tranquillizing drugs[248,249]. One potent inhibitory class was that of cyclopropylamines of which tranylcypramine (**164**) (*trans*-2-phenylcyclopropylamine) was a successful, albeit clinically dangerous and eventually unusable agent[250]. Tranylcypramine (**164**) and analogous cyclopropylamines turn out to

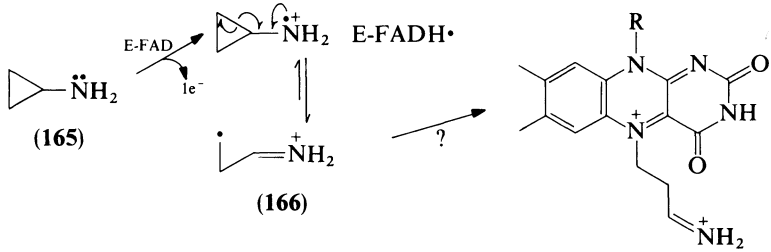


(**164**)

be suicide substrates for MAO. A number of studies[250–252] have suggested that monoamine oxidase may oxidize amine substrates by one-electron routes via amine radical cations and corresponding enzyme bound flavin coenzyme semiquinone (equation 31). This catalytic

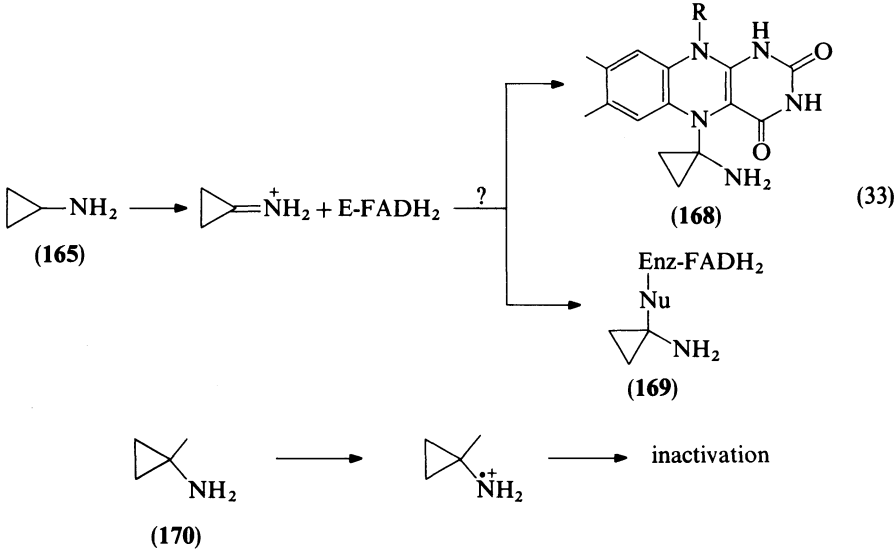
$$\underset{\text{E-FAD}}{RCH_2\ddot{N}H_2} \xrightarrow[\text{transfer}]{1e^-} \underset{\text{E-FADH}\bullet}{RCH_2\dot{\overset{+}{N}}H_2} \xrightarrow[\text{transfer}]{1e^-} \underset{\text{E-FADH}_2}{RCH{=}NH} \tag{31}$$

route with cyclopropylamine (**165**) could lead to alternative breakdown or covalent capture of the intermediate substrate radical (**166**) at a carbon-centered site to yield a covalent flavin adduct (**167**) (equation 32) and cause the observed time-dependent activity



(**165**) (**166**) (**167**) (32)

loss. The inactivation with cyclopropylamine (**165**) suicide substrates appears to lead to modified flavins but these can be labile and a complete structure of inactivated enzyme awaits. For example, an alternative route for inactivation would be net two-electron oxidation to the cyclopropylimine (**166**) equivalent which could then accumulate as tetrahedral adduct to the $FADH_2$ (**168**) or to some nucleophilic active-site residue (**169**) (equation 33)[251]. To distinguish between the two schemes and against the latter possibility studies with α-methylcyclopropylamine (**170**) showed MAO inactivation; in this case N-oxidation (and one-electron routes) but not imine formation is possible[253].



(33)

2. *Liver microsomal cytochrome P_{450} monooxygenases*

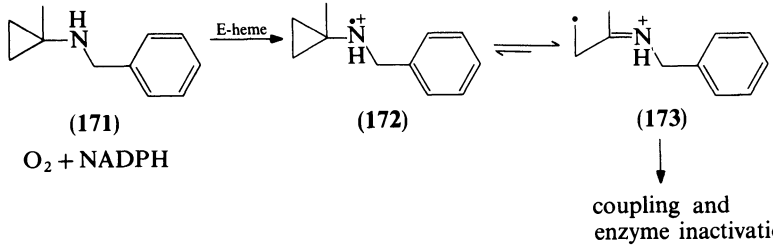
Cytochrome P_{450} monooxygenases are heme iron-based catalysts with capacity to oxygenate a range of cosubstrates[254]. There are several isoenzymic forms in liver endoplasmic reticulum including a major form inducible by exposure to phenobarbital. This isozyme is active for C,N,O and S hydroxylation against a wide range of substrate types and is a major catalyst for xenobiotic processing in animals[255]. Much mechanistic study and analysis has led to the proposal of one-electron oxidation of substrates prior to oxygen transfers[254]. Amine containing substrates can be processed for N-oxygenation (equations 34, 35) or, in the case of *N*-methyl- and *N*-ethyl-substituted substrates, for N-dealkylation by C_α-hydroxylation and subsequent decomposition of the tetrahedral product (equation 36)[256]. Studies with substituted cyclopropylamines, such as *N*-benzylcyclopropylamine and *N*-benzyl-α-methylcyclopropylamine (**171**), have shown

$$\mathrm{R{-}\underset{\displaystyle H}{\underset{|}{N}}{-}R' + O_2 + NADPH \rightarrow R{-}\underset{\displaystyle OH}{\underset{|}{N}}{-}R' + NADP^+ + H_2O} \tag{34}$$

$$\mathrm{R{-}\underset{\displaystyle R''}{\underset{|}{N}}{-}R' + O_2 + NADPH \rightarrow R{-}\overset{\displaystyle O^-}{\overset{|}{\underset{\displaystyle R''}{\underset{|}{\overset{+}{N}}}}}{-}R' + NADP^+ + H_2O} \tag{35}$$

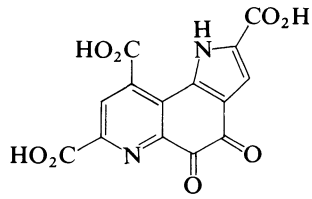
$$\mathrm{R{-}\underset{\displaystyle H}{\underset{|}{N}}{-}CH_3 + O_2 + NADPH \rightarrow R{-}\underset{\displaystyle H\ OH}{\underset{|\ \ |}{N}}{-}CH_2 \rightarrow RNH_2 + CH_2O} \tag{36}$$

time-dependent inactivation for this P_{450} isozyme[257,258] and strongly support the one-electron route with opening of the cyclopropylamine N-centered radical (**172**) to the acyclic carbon-centered alkyl radical (**173**) which is responsible for the subsequent enzyme inactivation. The structure of the inactive enzyme adduct has yet to be determined to further confirm this mechanistic rerouting of these cyclopropyl analogs of the normal amine cation radical to enzyme autoinactivation.



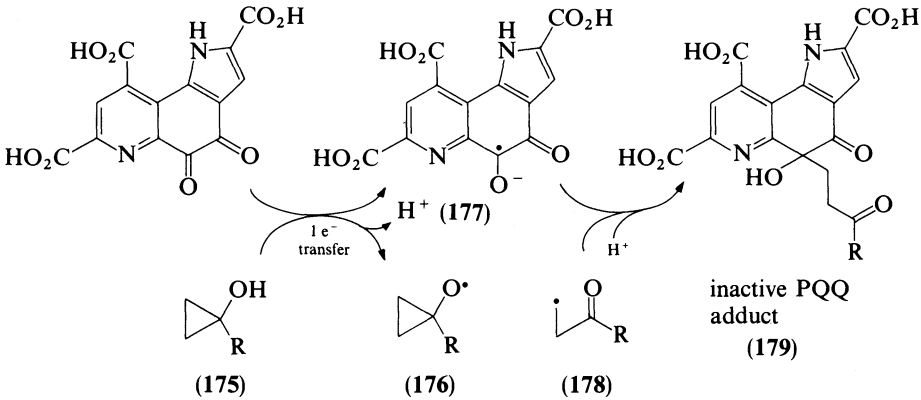
3. *Quinoprotein dehydrogenase*

The third case for likely enzymatic generation of an α-cyclopropyl radical or a cyclopropanone equivalent leading to target enzyme destruction is in the oxidation of cyclopropanol by certain bacterial alcohol dehydrogenases which have a novel type of redox coenzyme stoichiometrically bound and required for catalysis. The coenzyme has been termed pyrroloquinoline quinone (PQQ) (**174**)[259] or methoxatin and the trivial name



(**174**)

for such proteins has been unofficially proposed to be quinoproteins[260]. Mincey and coworkers[261] reported that cyclopropanol (**175**) inhibits such a quinoprotein methanol dehydrogenase but inactivation occurred with incorporation into inactive enzyme of only 0.14 radiolabel equivalents, suggesting only 14% of the isolated enzyme molecules were active. More recently Dijkstra and coworkers[262] reported that the corresponding enzyme from *Hyphomicrobium X* was inactivated with full stoichiometric incorporation of

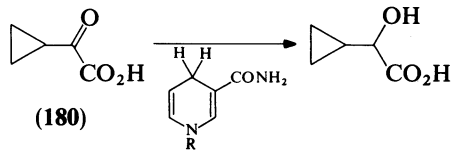


(37)

cyclopropanol-derived radioactivity. Although the structure of the inactive PQQ-substrate has not yet been determined, their proposal is one-electron transfer to yield the cyclopropanol radical (**176**) and PQQ semiquinone (**177**), ring-opening of the cyclopropyl system to the propionaldehyde β-carbon (**178**) radical and then radical recombination to yield a modified inactive PQQ adduct at the enzyme's active site (equation 37).

C. Cyclopropane Models for NADH Redox Transfer Mechanisms

A final example focusing on the use of cyclopropylcarbinyl integrity or fragmentation as a diagnostic observation for two- vs. one-electron transfer is in probes of NADH-type redox processes. Suckling and coworkers[263] showed dihydronicotinamide reduction



(**180**)

of cyclopropane glyoxylic acid (**180**) without fragmentation. Also *N*-(cyclopropylmethylene)phenylamines, cyclopropyl z-pyridyl ketones, and ethyl cyclopropylmethylenepyruvate[264] have been reduced by dihydronicotinamides with no fragmentation of the cyclopropane groups. In contrast, and as one-electron pathway controls, reduction of these molecules by tin hydrides induces the quantitative ring-openings anticipated for the radical mechanisms. These data strongly support hydride transfer mechanisms for these NADH model reactions and thereby for the enzymatic cases as well.

V. SUMMARY

This chapter began by surveying the rich diversity of naturally occurring structures which contain stable and isolable cyclopropane rings. Both in compound types (e.g. steroids, alkaloids, amino acids) and in cyclopropane substitution patterns, the cyclopropyl group is no doubt an ubiquitious functional group present in many biogenetic molecules. Additionally this three-membered ring moiety is present in molecules with diverse oxidation states including methylene cyclopropanes, cyclopropylamino acids, methylene cyclopropylamino acids, cyclopropenes, cyclopropanones and even a very recent example of a cyclopropenone, detected in an antibiotic screen.

In addition to the stable cyclopropyl-containing metabolites that accumulate in cells and tissues, there is excellent evidence that the cyclopropyl group is often an obligate staging device in a biotransformation. We noted the laurinterol (**36**) to aplysin (**35**), thujopsene (**37**) to widdrol (**38**), and ergosterol precursor (**44**) to $\Delta^{5,7}$-diene (**41**) as three such processes where the cyclopropanes play a crucial role during the conversion. The first two by facile cyclopropylcarbinyl cation rearrangements, the latter by proposed transient generation then regiospecific fragmentation of a cyclopropanol to effect a net $\Delta^8 \rightarrow \Delta^7$-ene migration and redox isomerization at C(5).

The crucial intermediacy of cyclopropylcarbinyl species in the biological synthesis of hundreds (thousands) of steroids, carotenoids, retinoids and derivatives is exemplified by the C_{30} presqualene pyrophosphate (**77**) and the C_{40} prephytoene pyrophosphate (**89**). In the biosynthetic construction of the key C(1)–C(1) carbon–carbon in head-to-head joining of C_{15} or C_{20} alkyl alcohol pyrophosphate esters, the cyclopropylcarbinyl strategy via a formal insertion of C(1) of one monomer into the C(2)–C(3) double bond of the second monomer appears to be the central mechanistic solution in the biochemical inventory. The cyclopropylcarbinyl pyrophosphate forms as obligate intermediate whether the final

acyclic polyene is sp^2–sp^2 hybridized (phytoene, **88**) or reductively joined, sp^3–sp^3 hybridized (squalene, **76**). This brings the cyclopropyl group into center stage metabolically.

In the biogenesis of the three-membered ring system, the majority of cases reported employ cation-induced cyclizations. But other ring formation modes are also possible, such as anion-induced cyclization in the enzymatic conversion of *S*-adenosylmethionine (**99**) to 1-aminocyclopropane-1-carboxylate (**9**), photo-induced cyclization of a hexatriene precursor (**123**) to crispatene (**2**), and a series of cases where nucleophilic addition–elimination pathways are proposed to account for observed stereochemistry and/or skeletal connectivity, e.g. squalene to cycloartenol (**93**). In most of these cases, the state of analysis has been biosynthetic tracer study with regio- and stereospecifically labeled precursors and analysis, often elegant and subtle, of isotope fate and steric desperation. With few exceptions there has been no effort or no progress on cyclopropanation enzyme isolation, characterization, or analysis, so intimate mechanistic understanding of the biochemical process is lacking. Thus, one cannot be sure all conversions are *even enzyme-catalysed*, especially in the acid-susceptible rearrangements of some plant secondary products. State of the art enzymology coupled when advantageous with gene cloning and expression studies would be very fruitful here.

Given cation-, anion-, and photo-induced construction of biological cyclopropane structures, what about metabolic breakdown. routes? Here, the nucleophilic addition–elimination mechanism and the radical-fragmentation initiated via α-amine cation radical formation, seem to be the pathways in the metabolic processing of 1-aminocyclopropane-1-carboxylate (**9**) to α-ketobutyrate (**138**) in bacteria and yeast or to ethylene (**139**) in plants, respectively. The ethylene generation in particular is both a mechanistic intriguing oxidative fragmentation, converting as it does the α-carbon of the amino acid to cyanide ion in the process, and also a physiologically consequential one since ethylene (**139**), simple structure though it is, is both a fruit-ripening and wound-healing hormone in plants.

Ethylene formation is fastidiously controlled in plants (as are other hormone productions) and the oxidative conversion of sp^3-hybridized C(3) and C(4) of methionine to sp^2-hybridized ethylene (**139**) via the (now you see it, now you don't) three-membered ring mechanism is a pretty act of metabolic functional group conjuring.

The last section of this chapter analyzed a topic likely to be a burgeoning one in the near future; the use of the cyclopropyl group as a sensitive mechanistic probe of enzymatic processes, either to reroute catalytic turnover to a tell-tale acyclic product and/or to generate a mechanism-based inactivator for a given target enzyme. Thus functionalized cyclopropanes, in the guise of the methylenecyclopropyl group (of **7**) to anion site in acyl CoA dehydrogenase action, in the guise of the blocked hemiaminal of coprine (**29**) as precursor to the killing cyclopropanone equivalent (**160**) for aldehyde dehydrogenase, and in the guise of cyclopropylamine equivalents as radical traps for monoamine oxidase, cytochrome P_{450} monooxygenase, and quinoprotein alcohol dehydrogenase, are enzymically activatable, mechanism-driven, covalently modifying specific enzymatic suicide substrates.

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CHAPTER 17

Preparation and uses of isotopically labeled derivatives

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I. INTRODUCTION

The charge to the author of this chapter was to describe the preparation and uses of cyclopropanes, cyclopropenes, and methylenecyclopropanes that were isotopically labeled either directly on the ring or on an atom attached to the ring. The following text is an attempt to fulfil that mandate. The material covered is by no means encyclopedic; it is intended to be representative, but it undoubtedly reflects in part the biases and limitations of the author. Readers who find their own work to be relevant but absent should interpret the omission to be an indication of the author's ignorance, not of his judgement of the quality of the science. The disproportionately large section devoted to thermal rearrangements does, in part, reflect the relative use of labeled cyclopropanes in those reactions compared to the other types covered in this chapter, but might also be another indication of the author's relative familiarity with the material.

The section on synthesis has been limited to preparations of a particular type of labeled cyclopropane, for reasons detailed in Section II. The 'uses' of labeled cyclopropanes have been interpreted in an almost exclusively mechanistic sense. Within this context reactions involving labeled cyclopropanes as reactants, intermediates, or products have been considered. Finally, it is worth noting that the definition of the material to be included in this chapter has sometimes resulted in a rather artificial selection of material on related mechanistic problems. Those readers who have carried out elegant mechanistic work with cyclopropanes that did not happen to carry isotopic labels at the positions specified above should therefore not feel slighted by the omission of their work.

The literature is covered through March 1985.

II. SYNTHETIC METHODS

It is, of course, in the nature of isotopic labeling that the synthetic methods for preparation of the requisite compounds be the same as those for their unlabeled analogues—the presence of the isotopic label will rarely be enough of a chemical perturbation to alter the course of the reactions. The only change that might need to be made is to modify the synthesis to make use of commercially available isotopically labeled starting materials. There is, however, one circumstance in which synthesis of isotopically labeled compounds can be significantly more difficult than preparation of their unlabeled relatives, that is when the presence of the isotopic label (usually a deuterium or tritium) creates a new chiral center in the molecule and the compound is required in only one of its two possible diastereomeric (or, worse still, enantiomeric) forms. Since separation of compounds differing only in the location of an isotopic label is, with rare exceptions, impossible with current technology, preparation of such materials requires the use of reactions that introduce labels with high stereoselectivity and maintain the stereochemistry throughout the synthetic sequence. The sections that follow (II.A–F) deal exclusively with such reactions, as applied to the preparation of cyclopropanes and methylenecyclopropanes with deuterium directly attached to the ring. Cyclopropenes are not included because the topology of such molecules prevents the existence of diastereomers, and, at least to the knowledge of this author, no work on the preparation of optically active cyclopropenes-3-d has been reported.

A. Carbene or Carbenoid Addition to Stereospecifically Deuterated Alkenes

Since cycloaddition of singlet carbenes and carbenoids to alkenes appears to be highly stereoselective[1], one can introduce a deuterium label into either of the two diastereotopic sites on the methylene of a substituted cyclopropane by cycloaddition to the corresponding *E* or *Z* deuterated alkene. The labeled alkenes can, in turn, usually be prepared by reduction of the corresponding alkyne with diisobutyl aluminum hydride[2] (DIBAL), a hindered borane[3] such as 9-BBN (9-borabicyclo[3.3.1]nonane), or triphenyltin hydride[4]. Reduction of the unlabeled alkyne and quenching with D_2O gives the *E*-alkene, while reduction of the alkyne-1-d (easily prepared by exchange with D_2O under basic conditions) and quenching with H_2O gives the *Z* alkene. Preparation[5] of the 1,1-dibromo-2-phenylcyclopropanes-3-d shown in Figure 1 serves to illustrate the approach.

Application of this strategy to the preparation of stereospecifically labeled methylenecyclopropanes is not so straightforward. It is possible to carry out a stereoselective cycloaddition to a labeled alkene with a methylchlorocarbene equivalent[6] but the subsequent dehydrohalogenation with potassium *t*-butoxide can cause loss of stereochemistry if there is a substituent on the ring that would be even a mild carbanion stabilizer. The preparation of 2-phenyl-1-methylenecyclopropane-3-d is an example[5] (see Figure 2). In order to circumvent this problem it is necessary to take a more circuitous route that allows introduction of the C=C double bond by reductive elimination rather than base-promoted dehydrohalogenation. Figure 3 shows a successful route to *trans*-2-phenyl-1-methylenecyclopropane-3-d[5] starting with the appropriate dibromocyclopropane, prepared as shown in Figure 1.

B. The Haller–Bauer Reaction

The cyclopropanation of stereospecifically labeled alkenes (Section II.A) is a good way to make single diastereomers of a racemic labeled cyclopropane. Unfortunately it does not readily lend itself to the preparation of optically active labeled cyclopropanes because of

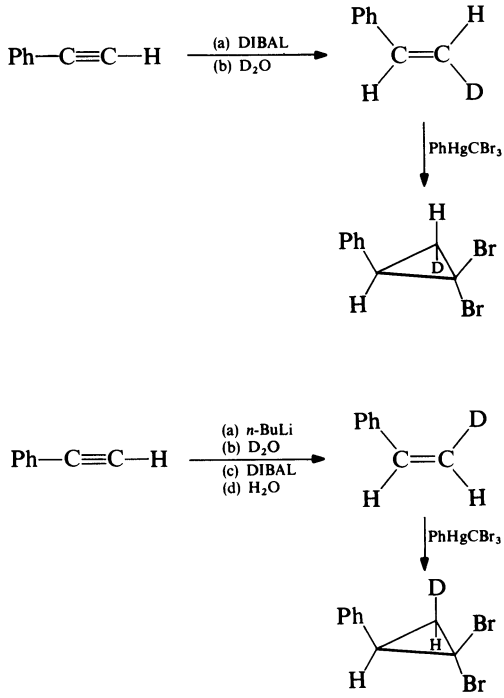


FIGURE 1

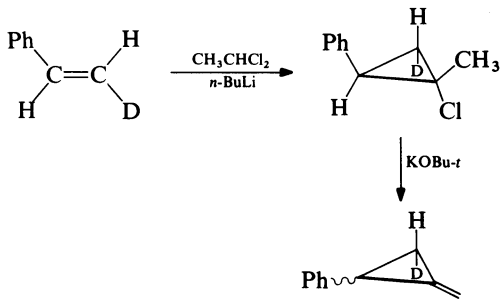


FIGURE 2

the achiral nature of most alkenes. (In principle an optically active cyclopropanation catalyst could be used but none seems yet to have been found that gives good optical purity[8].) The Haller–Bauer reaction is well suited to this problem because it involves the cleavage of a cyclopropyl phenyl ketone[9] which can, in turn, be prepared from a cyclopropanecarboxylic acid. The carboxylic acid function allows one to carry out an optical resolution with an alkaloid such as quinine or brucine. An example of the

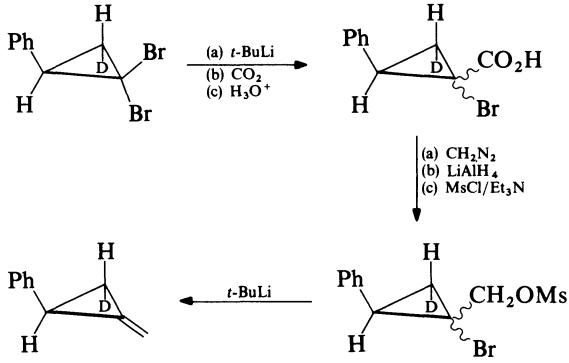


FIGURE 3

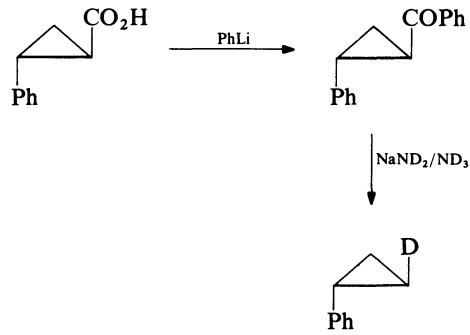


FIGURE 4

application of this procedure to the preparation of optically active, deuterated cyclopropanes comes from the work of Berson and coworkers[10] and is illustrated in Figure 4.

The cyclopropyl carbanion that presumably is involved in this reaction retains its configuration, probably because inversion causes increased ring strain (see Section VI).

C. Catalytic Decarbonylation of Aldehydes

A nice complement to the Haller–Bauer reaction (Section II.B) is the decarbonylation of aldehydes with $(Ph_3P)_3RhCl$ (Wilkinson's catalyst)[11]. A recent example comes from the work of Baldwin and Barden[12] and is shown in Figure 5. Interestingly, partial optical resolution was achieved in this synthesis by use of an optically active copper catalyst for the preparation of the labeled phenylcyclopropane carboxylic acid. The resolution to optical purity was then accomplished by recrystallization of the quinine salt of the acid.

D. Reduction of Halocyclopropanes

Gem-dihalocyclopropanes are readily prepared from the corresponding dihalocarbenes or dihalocarbenoids. Conversion of these compounds to cyclopropanes containing a deuterium label at a stereochemically defined site is relatively straightforward. Both

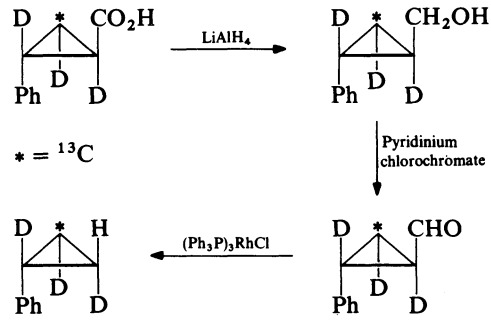


FIGURE 5

Bu_3SnH[13] (or Bu_3SnD) and alkali metal reduction[14] followed by H_2O (or D_2O) are effective. When the two halogens (bromine works better than chlorine) are diastereotopic it is quite often possible to remove them selectively under different conditions, thereby gaining access to both diastereomers of the product. Examples[15] are shown in Figure 6.

Reduction of vicinal dihalocyclopropanes has also been used to introduce deuterium labels stereoselectively[16]. The peculiar stereochemistry of this process (*all* stereoisomers of the original halocyclopropane give the same stereoisomer of the product) suggests that perhaps a cyclopropene might be formed which then undergoes electron transfer reduction under the conditions of the reaction (see Figure 7).

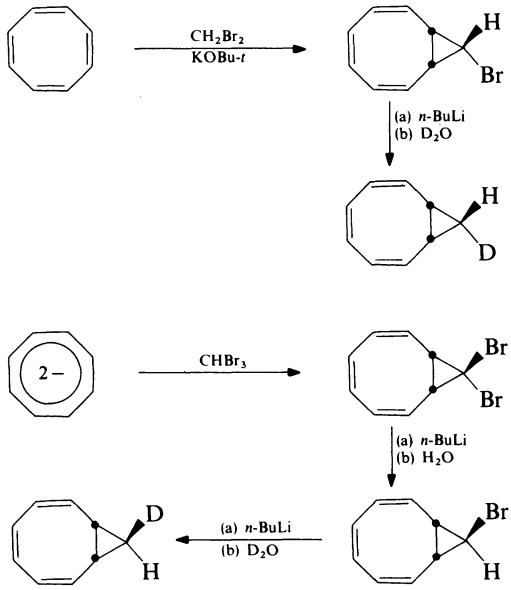


FIGURE 6

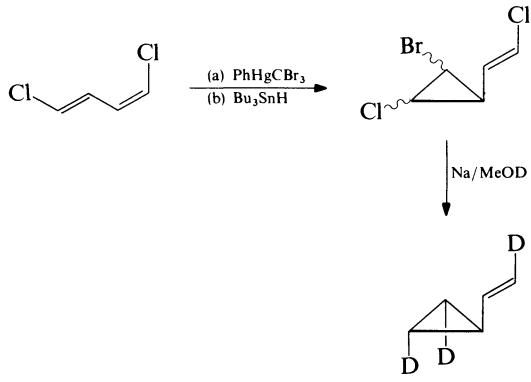


FIGURE 7

E. Cyclopropane Ring-closure by Stereoselective Nucleophilic Displacement

The predictable inversion of configuration that accompanies S_N2 substitution reactions can be used to convert stereoselectively labeled vicinal dihaloalkanes into stereoselectively labeled cyclopropanes. The dihaloalkanes can, themselves, be prepared by halogenation of stereoselectively labeled alkenes. Two examples are shown in Figure 8[17] and Figure 9[18].

F. Nucleophilic Addition to Cyclopropenes

A little-used route to stereoselectively labeled cyclopropanes is nucleophilic addition to the corresponding cyclopropene. Access to both labeled and unlabeled cyclopropenes from the corresponding 1-alkynes allows preparation of both diastereomers of the labeled product. This route is one of the few that would allow easy preparation of a 1,1-disubstituted-cyclopropane-2-d. Cyclopropanation of the corresponding alkene would in principle achieve the same goal but preparation of such alkenes with a label in a defined stereochemical position is not easy. An example of the approach is shown in Figure 10[19].

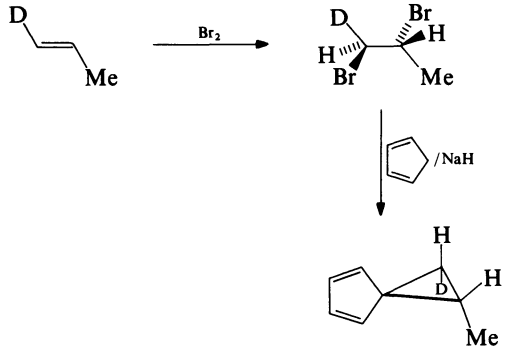


FIGURE 8

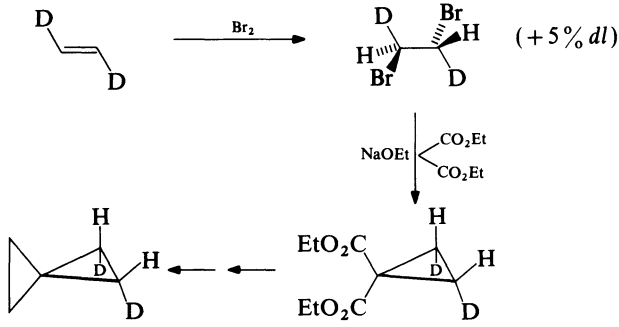


FIGURE 9

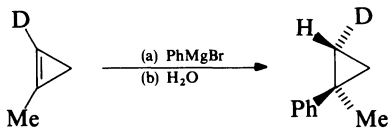


FIGURE 10

III. THERMAL REARRANGEMENTS

A. Stereomutation of Cyclopropanes

1. Formulation of the problem

Stereomutation is a term that encompasses *cis–trans* isomerization and racemization of substituted cyclic molecules. Its detection in cyclopropanes requires at least two substituents (either or both of which could be isotopic labels) on two different carbons.

Three mechanisms have been postulated for cyclopropane stereomutation; they are summarized in Figure 11. In the first, usually attributed to F. T. Smith[20], a single methylene is simply twisted around by 180°. Molecular orbital calculations by Kollmar[21] have suggested that this could be energetically feasible if one either stretched both of the C–H bonds on the rotating methylene (thereby making something like a cyclopropylidene–hydrogen complex) or, somewhat better, stretched both of the C–C bonds to the rotating methylene (creating a methylene–ethylene complex).

The second mechanism, suggested originally by Rabinovitch and coworkers[22] but later elaborated by (and usually attributed to) Benson[23] involves trimethylene, the biradical generated by homolysis of one C–C bond in cyclopropane, as an intermediate in the reaction. The thermochemical calculations of Benson suggested that this intermediate might sit in a potential energy well some 9 kcal mol^{-1} deep. Since the barrier to rotation about the $C–CH_2\cdot$ bonds would be expected to be much smaller than this, it followed that the intermediate should lose stereochemical information by essentially random rotation at both methylenes.

The third mechanism, suggested by R. Hoffmann[24] as a result of extended Hückel calculations, also involves trimethylene but gives it special properties that would lead to correlated conrotation of the terminal methylenes. Specifically, the calculations suggested that the C–H σ bonds of the central methylene could be used as a kind of pseudo-p_π-orbital

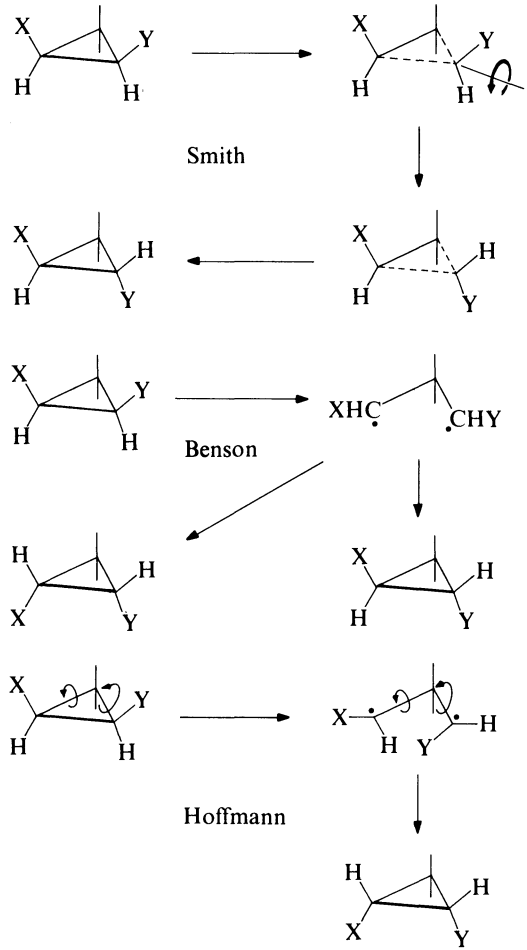


FIGURE 11

that would allow direct, 'through bond', conjugation of the orbitals containing the unpaired electrons. This interaction was found to lead to a preference for formation and closure of trimethylene by concerted conrotation at two methylenes. Subsequent more sophisticated calculations of both the potential energy surface[25, 26] and the trajectories of molecules across the potential energy surface[27] supported Hoffmann's proposal.

Operational distinction among the three mechanisms comes from an analysis of how a single event starting with a particular enantiomer of a 1,2-disubstituted cyclopropane can give the various possible products. For the Smith mechanism, a single event can interconvert *cis* and *trans* isomers but cannot interconvert enantiomers. Interconversion of enantiomers requires at least two operations of the Smith mechanism on different carbons. The Benson mechanism allows both *cis–trans* isomerization and interconversion of enantiomers by a single cleavage of the bond between the two substituents. The Hoffmann mechanism can interconvert enantiomers by a single cleavage of the C–C bond between the

substituents but can lead to *cis–trans* isomerization only by cleavage of a bond to the unsubstituted methylene.

The results that follow in Sections III.A.2–III.A.8 are from experiments designed to exploit this difference in an attempt to determine which, if any, of these mechanisms actually occurs. Other, equally elegant, experiments have been performed with the same goal but are not included here because they did not happen to involve isotopically labeled cyclopropanes.

2. *Stereomutation of* trans-*1,2-dimethyl-1,2-bis(trideuteriomethyl)cyclopropane*

Compound **1** was prepared in optically active form by Berson and Balquist[28]. Upon pyrolysis it suffered both racemization and *cis–trans* isomerization. If one assumes that only the bond between the two quaternary carbons will be cleaved and, further, that secondary equilibrium isotope effects are negligible (both of which seem like reasonable assumptions) then the operation of the three mechanisms can be summarized as shown in Figure 12. The mechanistic rate constants in this scheme are defined as follows: k_o is the rate constant for opening to the Benson biradical; k_c is the rate constant for closure of the Benson biradical to a particular enantiomer of the cyclopropane; k_1 is the rate constant for single rotation of either of the $C(CH_3)(CD_3)$ groups (i.e. the Smith mechanism); k_{12} is the rate constant for correlated double rotation of both $C(CH_3)(CD_3)$ groups (i.e. the Hoffmann mechanism). The kinetics of the problem can be solved explicitly by applying the steady state approximation to the biradical intermediate. The result is:

$$\frac{k_i}{k_\alpha} = \frac{4k_1 + k_o}{2k_1 + k_o + 2k_{12}} \tag{1}$$

The symbols k_i and k_α in equation 1 represent respectively the phenomenological rate constants for *cis–trans* isomerization and racemization. From this equation one can see that a pure Smith mechanism ($k_o = k_{12} = 0$) would give $k_i/k_\alpha = 2$. A pure Benson mechanism ($k_1 = k_{12} = 0$) would give $k_i/k_\alpha = 1$. Finally, a pure Hoffmann mechanism ($k_i = k_o = 0$) would give $k_i/k_\alpha = 0$.

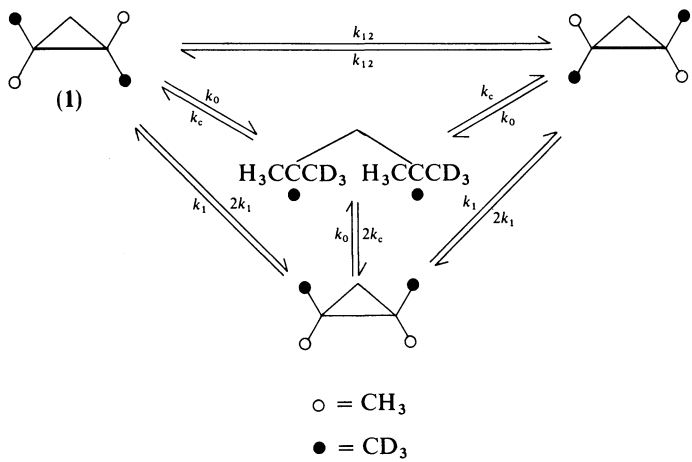


FIGURE 12

The experimental result was $k_i/k_\alpha = 1.74$ at 350.2°C. This result shows that either none of the above mechanisms is correct or that some mixture of them is occurring, with at least some component of the Smith mechanism included (in order to make the ratio > 1). A convenient explanation, suggested by Berson and Balquist[28], would be that homolysis of the 1,2 bond to give the biradical does occur but that the biradical suffers neither rapid random rotation as required by the Benson mechanism nor correlated double rotation as required by the Hoffmann mechanism. Instead, they propose, it could suffer recyclization at a rate somewhat greater than rotation (the data would be fit by a ratio of about 11 : 1 for recyclization : rotation rate constants). If this were the explanation, it would seem to suggest that the biradical did not exist in as deep a potential energy well as suggested by the Benson calculations for the parent trimethylene. It is also worth noting, as Berson and Balquist did, that the presence of the sterically bulky methyl groups might artificially disfavor the Hoffmann mechanism since correlated double rotation would inevitably introduce a severe steric interaction between methyls on opposite ends of the biradical.

A similar conclusion, i.e. intermediacy of a biradical that rotated at a rate comparable with the rate of its recyclization, was reached by Carter and Bergman from a study of optically active 1-methyl-2-ethylcyclopropanes[29]. This study will not be described in detail here because it did not include an isotopically labeled cyclopropane.

3. *Stereomutation of optically active* trans-*cyclopropane-1,2-d_2*

The ultimate test of the theoretical predictions for the mechanism of cyclopropane stereomutation would be to use an optically active disubstituted cyclopropane in which the substituents were just isotopes of hydrogen. This is a challenging problem both from a synthetic standpoint and from an analytical one. The analytical difficulty is particularly acute because one has to analyze a small, volatile molecule for both optical purity and *cis–trans* isomer ratio, and both measurements have to rely solely on the difference between isotopes. There are no functional groups to be used as 'handles' for an optically active NMR shift reagent and so determination of optical purity must come from direct measurement of rotations—with a probable maximum specific rotation of < 1 °!

Despite these enormous experimental difficulties, Berson and Pedersen[30] accomplished the task, using *trans*-cyclopropane-1,2-d_2. The synthesis was carried out as described in Section II. The analysis of *cis–trans* isomer ratios was effected by quantitative IR spectrometry, and the rotations were measured on the pure liquid cyclopropane in a specially designed cell.

Even the kinetic analysis is more complicated for this molecule than for the tetramethylcyclopropane described above. One must now consider cleavage of all three cyclopropane bonds instead of just the one between the substituents. This means that even the Hoffmann mechanism can lead to *cis–trans* isomerization in a single step by cleavage of a CHD–CH_2 bond. The full mechanism is shown in Figure 13.

Despite the apparent complexity, the kinetics of this reaction can be solved analytically provided one applies the steady state approximation to each of the three biradicals[31]. The result is:

$$\frac{k_i}{k_\alpha} = \frac{4k_1 + k_o(2 + 1/z_o) + 4k_{12}}{2k_1 + k_o(1 + 1/z_o) + 2k_{12}(1 + 1/z_{12})} \tag{2}$$

The mechanistic and phenomenological rate constants in equation 2 have the same meanings as those in equation 1; z_o and z_{12} are the mechanistic secondary isotope effects for formation of the biradical and correlated double rotation respectively.

If one ignores secondary isotope effects (i.e. z_o, $z_{12} = 1.00$) then the predicted values of k_i/k_α are 2.00, 1.50 and 1.00 for the Smith, Benson and Hoffmann mechanisms respectively. If one assumes a normal (α) secondary isotope effect of about 1.1 then the predictions

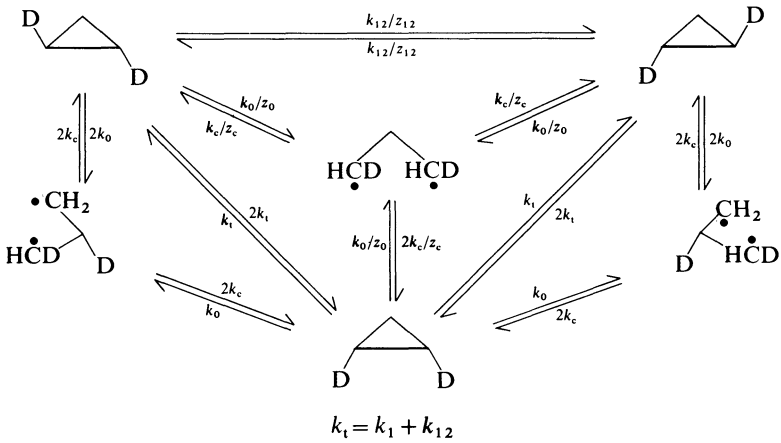


FIGURE 13

become 2.00, 1.52 and 1.05. Experimentally, Berson and Pedersen found $k_i/k_\alpha = 1.04 \pm 0.07$, in excellent agreement with the expectation for the Hoffmann mechanism with a normal secondary isotope effect.

Subsequently Baldwin and Carter suggested that the dominant secondary isotope effect might be of the β type rather than the α type assumed above[32]. If this were true the values of z_0 and z_{12} would be < 1. However, in order for such an effect to make any qualitative change in the preferred mechanism it would be necessary to postulate an absurdly large β isotope effect of > 13 (or $< 1/13$ for z_0 and z_{12}).

Even with the uncertainty in isotope effect, then, Berson and Pedersen's experiment seems to be most consistent with the Hoffmann mechanism.

4. Stereomutation of labeled phenylcyclopropanes

One of the nice features of the synthesis used by Berson and Pedersen to prepare optically active *trans*-cyclopropane-1,2-d_2 is that it involved synthesis of optically active *trans*-phenylcyclopropane-2-d as an intermediate. It was thus possible from one synthetic sequence to determine not only the mechanism of stereomutation of the dideuterated cyclopropane but also to find out what effect, if any, a phenyl substituent had on the mechanism.

Kinetic analysis of the phenylcyclopropane-2-d stereomutation is still more complicated than that of cyclopropane-1,2-d_2 because now both *trans* and *cis* isomers are chiral. The lower symmetry of the molecule leads to an increase in the number of both mechanistic and phenomenological rate constants. Unfortunately the increase in the former is larger, meaning that the problem becomes under-determined. The number of mechanistic parameters can be reduced by recouching the problem in terms of total numbers of single and correlated double rotations, with the recognition that it will not then be possible to distinguish single rotations that are part of the random motion of a Benson biradical from the single rotations of the Smith mechanism. A similar ambiguity exists for the Hoffmann and Benson mechanisms when one considers total numbers of correlated double rotations.

Even with this simplification, for the scheme which is shown in Figure 14, the problem remains under-determined. Thus it is not possible to separate k_2, the rate constant for single rotation of the deuterated methylene, from k_{23}, the rate constant for correlated

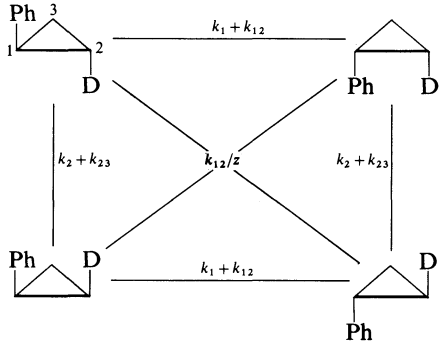


FIGURE 14

double rotation at the deuterated and undeuterated methylenes[31]. Nevertheless, it was possible from the experimental determination of rate constants for *cis–trans* isomerization and racemization to assign the following values to the mechanistic rate constants (at 309.5 °C):

$$k_1 = 0.0$$

$$k_{12} = 9.6 \times 10^{-6}\,s^{-1}$$

$$k_2 + k_{23} = 1.9 \times 10^{-6}\,s^{-1}$$

Thus the dominant process was still found to be a correlated double rotation.

Berson and coworkers[33] followed this study with a related analysis of the stereomutation of phenylcyclopropane-2,3-d_2. In this system one can separate k_2 from k_{23} but cannot separate k_1 from k_{12}. However the two studies together would, in principle, allow complete determination of all of the mechanistic rate constants. In the event, experimental difficulties did not allow this complete dissection of the rate constants. The study did, however, provide an independent measure of k_1, which was found here to be $0.15 \times 10^{-6}\,s^{-1}$, again showing correlated double rotation to be by far the dominant process for stereomutation at C(1).

Interestingly, this is not the end of the story. Recently, Baldwin and coworkers[34] have reported an ingenious experiment involving the stereomutation of (1*R*,2*S*,3*R*)-phenylcyclopropane-2-^{13}C-1,2,3-d_3. In this experiment the phenylcyclopropanes from a stereomutation experiment were derivatized by oxidation of the benzene ring to a carboxylic acid followed by treatment with phenyl lithium to give the phenylcyclopropyl ketone. This process introduced a heteroatom to which an optically active lanthanide shift reagent could be coordinated, allowing determination of optical purities by NMR. The ^{13}C label allowed the stereochemistry at each carbon to be determined by splitting the signal for the proton on C(2), thereby separating it from that of the proton on C(3). With this technique, it was possible to determine the magnitudes of each of the individual mechanistic rate constants.

The results (at 309.3°C) were:

$$k_1 = 3.6 \times 10^{-6}\,s^{-1}$$

$$k_2 = 8.7 \times 10^{-6}\,s^{-1}$$

$$k_{12} = 2.0 \times 10^{-6}\,s^{-1}$$

$$k_{23} = 0.0$$

in other words *very* different from those of the Berson group. According to these results the single rotation processes are dominant!

In fact the results are not quite as dramatically different as they appear when presented this way. The mechanistic rate constants are derived from phenomenological rate constants that can be described as linear combinations of the mechanistic ones. The discrepancy between the two results can be traced to a difference in just one of the phenomenological rate constants—the one corresponding to the first order loss of optical activity for a 1 : 1 mixture of (1*R*,2*S*)- and (1*R*,2*R*)-phenylcyclopropane-2-d. The peculiar feature of this problem is that the Berson group obtained an internally consistent set of results from two independent experiments[31a, 33] with one value for this rate constant and the Baldwin group also obtained an internally consistent set from two independent experiments[34, 35], but with a value that differed by a factor of 2.7 from that found by the Berson group. It is hard to know how to reconcile such results and so, to be objective, one must probably say that despite the immense amount of effort put into the problem the mechanism of stereomutation of phenylcyclopropane remains something of a mystery.

5. *Stereomutation of vinylcyclopropane-2,3-d_2*

In 1969 Willcott and Cargle[36] reported experiments in which they prepared and pyrolyzed 1-(2-deuteriovinyl)cyclopropane-*trans*, *trans*-2,3-d_2 (see Figure 15). They found that the other stereoisomers of this compound were formed at equal rates, consistent with the expectation for a Benson-type biradical sitting in a potential energy well of substantial depth.

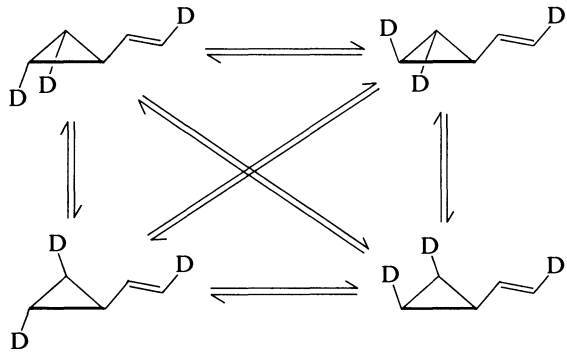


FIGURE 15

If one recasts this result in terms of rate constants for single and double rotations, the finding is $k_1 = k_2 + k_{12}$, that is one-center epimerization at the vinyl-bearing carbon appears to be dominant. This is because loss of stereochemistry at the vinyl-bearing carbon can occur by cleavage of either of two bonds whereas loss of stereochemistry at either of the deuterated carbons requires cleavage of one specific bond (assuming that cleavage of the bond between the deuterated carbons is negligible). The relationship between the mechanistic rate constants for one- and two-center epimerizations is not consistent with either of the results obtained for the epimerization of labeled phenylcyclopropanes. Thus, assuming that one of the two sets is correct, there appears to be a substantial difference between a phenyl and a vinyl substituent—a rather surprising conclusion given the quantitatively similar effects that they have on radical stabilization[37].

6. Stereomutation of 2-phenylcyclopropane-1,3-d_2-1-carbonitrile

A careful study of the stereomutation of 2-phenylcyclopropane-1,3-d_2-1-carbonitrile by Baldwin and Carter[38] revealed that the reaction could be identified with exclusive cleavage of the bond between the two substituents. Thus the absolute configuration of the CHD carbon (C(3)) did not change, as indicated in Figure 16.

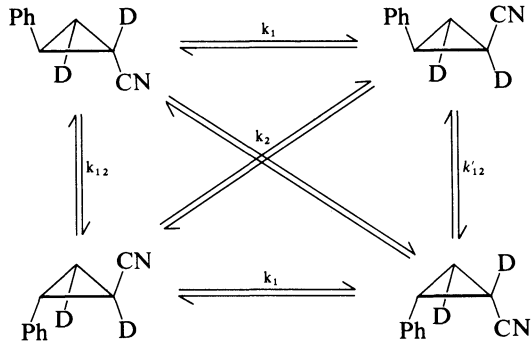


FIGURE 16

The change in concentration of the four species in Figure 16 as a function of time could be fit by assigning the following values to the mechanistic rate constants (at 242.1°C):

$$k_1 = 0.76 \times 10^{-5}\ s^{-1}$$
$$k_2 = 0.33 \times 10^{-5}\ s^{-1}$$
$$k_{12} = 0.60 \times 10^{-5}\ s^{-1}$$
$$k'_{12} = 0.43 \times 10^{-5}\ s^{-1}$$

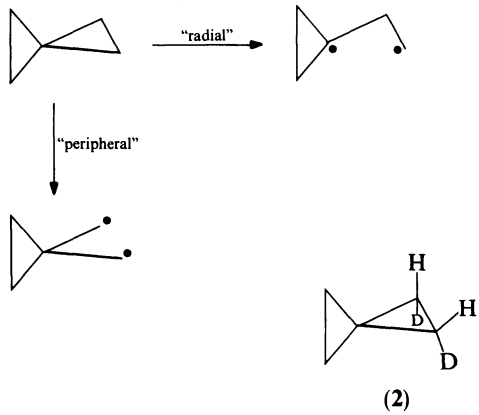
The equilibrium constant for isomers with a *cis* and *trans* relationship between the phenyl group and the nitrile was found to be 0.40, [*cis*]/[*trans*].

These results show no clear preference for a single or double epimerization process. Perhaps even more surprising, they are *not* consistent with the intermediacy of a rotationally equilibrated biradical having trigonal planar geometry for the radical centers, because an intermediate of this kind would be effectively achiral (ignoring the deuterium on C(3)) and would therefore give the two 'enantiomers' (again, ignoring the label on C(3)) of the *cis* isomer in identical amounts. This would imply the equality $k_1 = k_2$, which does not seem to be satisfied within the likely experimental error.

It is not at all clear to this author why a vinyl substituent would lead to a biradical that was so long-lived that it lost all stereochemical information (see Section III.A.5) whereas a phenyl group and a nitrile with a combined radical-stabilizing effect some 10 kcal mol^{-1} *greater* than that of the vinyl[39] would not. Results like this make one suspect that the attempt to describe reaction mechanisms simply in terms of a potential energy surface connecting the various intermediates may not always be sufficient and that dynamic phenomena—the way in which molecules move across the surface—might sometimes play an important role. See Section III.C.5 for a further discussion.

7. Stereomutation of spiro[2.2]pentane-2,3-d_2

It is interesting to speculate whether homolysis of a 'radial' (1,3) or a 'peripheral' (1,2) bond in spiropentane would lead to the more stable biradical. The intermediate from



(2)

FIGURE 17

cleavage of a radial bond would be tertiary at one radical center whereas that from cleavage of a peripheral bond might enjoy cyclopropylcarbinyl stabilization (see Figure 17).

In 1969 Gilbert[40] showed that spiro[2.2]pentane-2,3-d_2 (2) underwent stereomutation with an activation energy of 51.5 kcal mol^{-1}. This is some 13 kcal mol^{-1} lower than that required for stereomutation of cyclopropane-d_2, a result which is really not consistent with radial bond cleavage because only 6–8 kcal mol^{-1} stabilization would be expected from conversion of a primary radical into a tertiary one[37] (and, in fact, a tertiary cyclopropyl radical would probably be less stabilized than a tertiary butyl radical because of the strain required to attain the near-planar geometry of a tertiary radical[41] in a cyclopropane ring).

Further support for preferential cleavage of the peripheral bond came from several later studies on substituted spiropentanes[42].

The stereomutation study of Gilbert showed that some *cis–trans* isomerization occurred[40]. This fact, taken in combination with the conclusion of preferential 1,2 bond cleavage, requires at least some one-center epimerization to have taken place. The ratio of one-center to two-center epimerization and the question of whether the intermediate is a geometrically equilibrated biradical cannot be determined from the data because no studies on resolved optical isomers were carried out with this compound. The later studies on the substituted spiropentanes were not found to be consistent with the intermediacy of a geometrically equilibrated biradical[42].

8. Stereomutation of 1-methylspiro[2.4]hepta-4,6-diene-d

The experimental results on cyclopropane stereomutation, such as those described in Sections III.A.2–7, have led to the fall from grace of the Smith mechanism (see Section III.A.1). One-center epimerizations are, these days, usually considered to arise from uncorrelated rotation in a trimethylene biradical. However, in 1976 Gilbert and Baldwin reported results on a system that was designed to favor the Smith mechanism as much as possible. The important contribution here was to recognize that Smith's mechanism of single methylene rotation would have as a transition state a structure containing planar tetracoordinate carbon. Gilbert and Baldwin argued that those structural features predicted theoretically to stabilize square planar carbon[43] would then be expected to maximize the probability for occurrence of the Smith mechanism. Since one of those

features was the presence of a ring containing 4n conjugated π electrons, they chose to investigate stereomutation of spiro[2.4]hepta-4,6-dienes[44].

Three phenomenological rate constants were obtained in three separate experiments (see Figure 18). The rate constant for racemization, k_α, was obtained from optically active 1-methylspiro[2.4]hepta-4,6-diene. The rate constant for *cis–trans* isomerization, k_{ct}, was obtained from racemic 1-methylspiro[2.4]hepta-4,6-diene-2-d. Finally, the rate constant for *syn–anti* isomerization of the cyclopentadiene ring, k_{sa}, was obtained from racemic 1-methylspiro[2.4]hepta-4,6-diene-4-d. This last experiment also served to reveal the existence of a competing process of stereomutation via [1,5]sigmatropic migration of the cyclopropane ring around the cyclopentadiene ring; fortunately it turned out to be more than an order of magnitude slower than the other processes at the temperature selected (221.1°C).

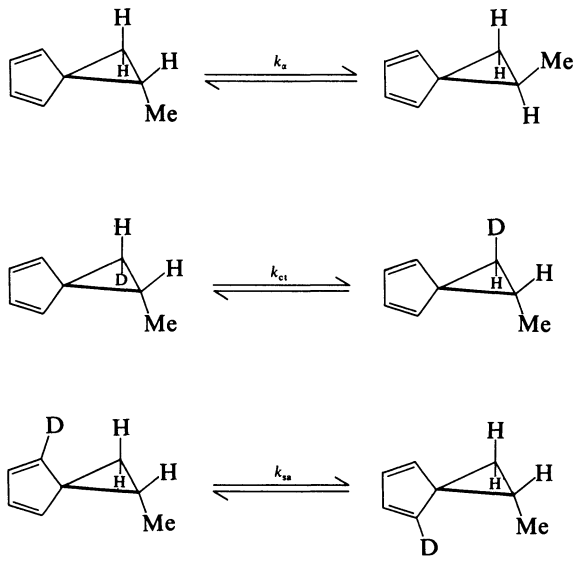


FIGURE 18

The three phenomenological rate constants, having the indicated experimental values, can be equated with combinations of mechanistic rate constants as follows:

$$k_\alpha = k_1 + k_{12} + k_{13} \qquad = (7.3 \pm 0.4) \times 10^{-5}\ \mathrm{s}^{-1}$$

$$k_{ct} = k_1 + k_2 + k_{13} + k_{23} = (7.2 \pm 0.5) \times 10^{-5}\ \mathrm{s}^{-1}$$

$$k_{sa} = k_1 + k_3 + k_{12} + k_{23} = (6.1 \pm 0.6) \times 10^{-5}\ \mathrm{s}^{-1}$$

As usual, the singly subscripted rate constants refer to one-center epimerizations and the doubly subscripted rate constants refer to two-center epimerizations at the carbons indicated by the numbers. There should, in principle, be a secondary deuterium isotope effect included in the mechanistic rate constants comprising k_{ct} but this would have its largest effect on k_{12} and k_{23} and the previous experience in cyclopropane stereomutations suggests that these are likely to be minor contributors at best.

If one wishes to ascribe the equality of k_α and k_{ct} to anything other than coincidence, it is necessary to set k_2, k_{12} and k_{23} equal to zero. It then follows that, since $k_{sa} < k_{ct}$, $k_3 < k_{13}$;

in other words the one-center epimerization at C(3), corresponding to the Smith mechanism with the stabilized transition state, is less important that the two-center epimerization at C(1) and C(3), corresponding to the Hoffmann mechanism or part of the motion of a Benson biradical. Thus one must conclude that either the theoretical predictions of stabilization of square planar carbon by inclusion in an aromatic ring are wrong, or that the Smith mechanism for cyclopropane stereomutation is so much less favorable than the other two that even this extra stabilization is insufficient to make it competitive.

B. The Cyclopropane—Propene and Related Rearrangements

Thermal conversion to propene was one of the first known reactions of cyclopropane[45]. Remarkably, however, the mechanism of this transformation is still a matter of some considerable uncertainty.

The problem is one of timing: a C–C bond has to be broken and a hydrogen has to be transferred from one carbon to another. Nobody suggests that the hydrogen relocation occurs first since this would involve the intermediacy of a structure with a pentacoordinate carbon, but there is considerable doubt about whether the C–C bond cleavage occurs first or whether it occurs in concert with the hydrogen migration. If the former mechanism were correct then it would appear that the stereomutation of cyclopropanes (Section III.A) and their structural isomerization might share a common intermediate—the trimethylene biradical (see Figure 19). Formation of this biradical could not be rate-determining for the structural isomerization, however, because it invariably occurs at a lower rate and with a higher activation energy than the stereomutation. In the case of methylcyclopropane-2,3-d_2, for example, the activation energy is 60.5 kcal mol^{-1} for the stereomutation and 62.3 kcal mol^{-1} for the structural isomerization[46].

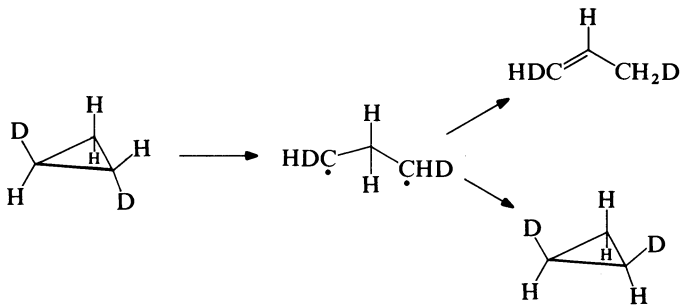


FIGURE 19

Isotope effect studies also support the idea of hydrogen transfer in the rate-determining step. Particularly noteworthy in this regard are the experiments and calculations of Rabinovitch and coworkers[47] who were able to reproduce the experimental intermolecular isotope effect for structural isomerization of cyclopropane-d_6, including its fall-off with decreasing pressure, by performing RRKM calculations that involved a transition structure with a partially transferred hydrogen. Calculations of this kind are not sufficiently sensitive, however, to be able to distinguish a transition state with a completely broken C–C bond (corresponding to hydrogen migration after trimethylene formation) from one with a partially broken C–C bond (corresponding to concerted hydrogen migration and ring cleavage).

Weak evidence in favor of a concerted mechanism comes from the observation that factors (such as substituents or fused small rings) that tend to weaken the C–C bond seem to increase the energy difference between stereomutation and structural isomerization[48]. One would think that if hydrogen migration occurred after biradical formation then the energy required to make the biradical would be irrelevant. On the other hand it would be consistent to suppose that the factors tending to weaken the C–C bond would have a greater influence on the stereomutation process than on a concerted structural isomerization involving a transition state with a C–C bond that was only partly broken.

C. The Vinylcyclopropane Rearrangement

1. *Formulation of the problem*

Formation of cyclopentene as one of the products of pyrolysis of vinylcyclopropane was first reported by Overberger and Borchert[49] and then was quantified by Flowers and Frey[50], who reported the activation parameters shown in Figure 20.

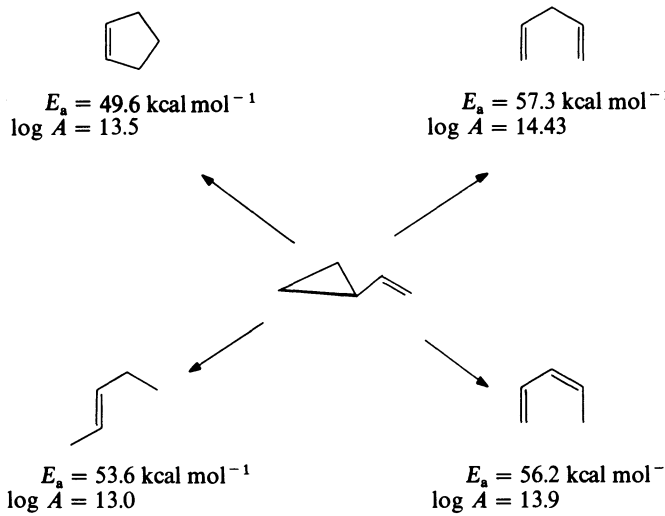


FIGURE 20

The products depicted in Figure 20 could all have come from a biradical that would be formed in the rate-determining step. In accord with this proposal would be the observations of Ellis and Frey[51], and Roth and König[52] on the rearrangement of *trans*-2-methylvinylcyclopropane, which was found to give 4-methylcyclopentene and (*Z*)-1,4-hexadiene (see Figure 21) in a ratio that was *constant* at $(11.60 \pm 0.12):1$, diene:cyclopentene, over a range of 59.5°C (from combination of the two sets of experimental data). The diene arises from stereomutation of the *trans* cyclopropane followed by fast homo-1,5-hydrogen migration either within the biradical or the *cis* cyclopropane (Figure 21). The temperature-independent product ratio implies that the rate-determining steps for cyclopentene formation and stereomutation have the same activation energy to within 0.2 kcal mol^{-1}. This would be consistent with the rate-determining formation of a common biradical, as shown in Figure 22. The only thing that is

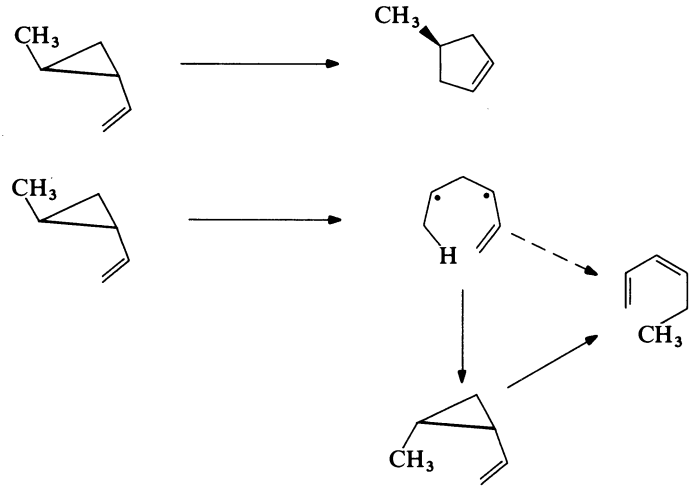


FIGURE 21

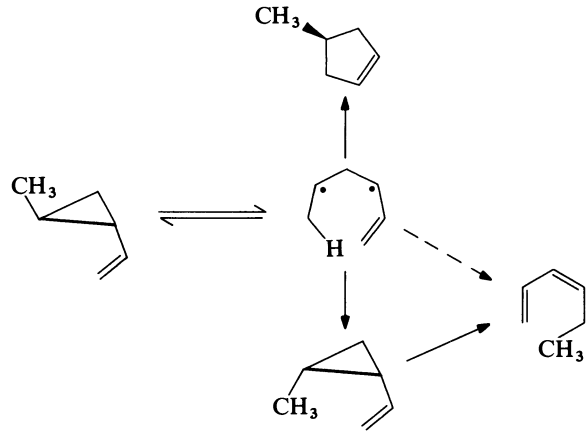


FIGURE 22

a little disquieting about such a mechanism is that one has a little trouble trying to draw a potential energy profile for it. The formation of the cyclopentene and of the diene from the biradical cannot have different activation energies because this would lead, again, to a temperature-dependent product ratio *even if formation of the biradical were rate-determining.* This problem will be addressed in more detail in Section III.C.5.

The real difficulties with the biradical interpretation began with the stereochemical studies on the cyclopentene formation. Early work was carried out by Mazzochi and Tamburin[53] and by Doering and Sachdev[54], then, in 1976, Andrews and Baldwin reported a study that allowed a complete stereochemical quadrisection of the vinylcyclopropane rearrangement of optically active *trans, trans*-1-methyl-2-propenylcyclopropane[55]. The four stereoisomeric 3,4-dimethylcyclopentenes formed in this reaction (see Figure 23)

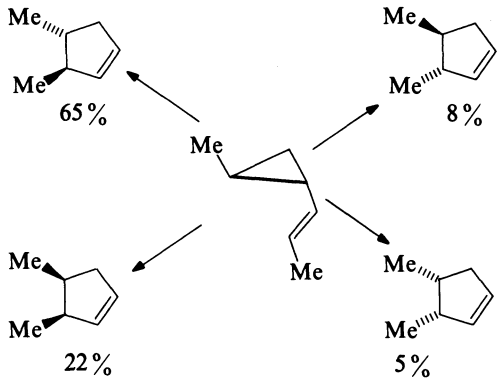


FIGURE 23

occurs as two pairs of enantiomers. If the reaction involved a geometrically equilibrated biradical the products should be racemic since the biradical would be achiral. In fact, as the results in Figure 23 show, the products were not racemic, or even close to it.

Here then is the dilemma: the thermochemistry suggests the intermediacy of a biradical in the vinylcyclopropane rearrangement but the stereochemical results do not seem consistent with what one might have imagined to be the equilibrium geometry of such an intermediate. It is against this background that the experiments involving isotopically labeled vinylcyclopropanes can be viewed.

2. *Vinylcyclopropane-2-d and -2,3-d_2*

In 1967 Willcott and Cargle reported[56] the pyrolysis and rearrangement of *trans*-vinylcyclopropane-2-d. They found that stereomutation occurred at least five times faster than rearrangement, a result that might seem inconsistent with the intermediacy of a common biradical for the two processes. It is important to note, however, that there are two geometrical isomers of the biradical, both of which can cause stereomutation but only one of which can allow ring expansion to the cyclopentene (see Figure 24). It is unlikely that the

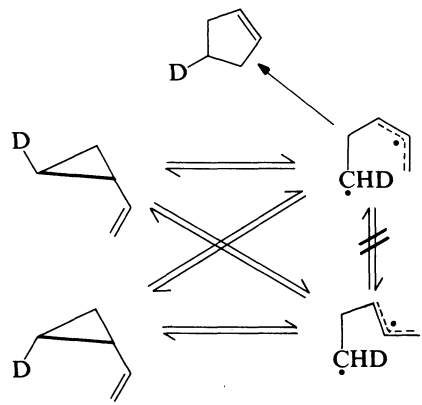


FIGURE 24

two isomeric biradicals would be able to interconvert once formed because it would require rotation about a partial double bond in an allyl radical, so all of the molecules giving the transoid biradical must necessarily return to starting material or suffer stereomutation.

As mentioned in Section III.A.5, the experiments of Willcott and Cargle on the related vinylcyclopropane-2,3-d_2 were deemed to be consistent with the intermediacy of a biradical that *was* geometrically equilibrated. This conclusion can now be seen to be very much at odds with the results of Andrews and Baldwin, mentioned in Section III.C.1.

3. *(R,R)*-trans-2-Methyl-1-(3,3-dimethyl-1-buten-1,1-d_2-2-yl)cyclopropane

Recently Gajewski and Warner have reported[57] an experiment designed to circumvent the mechanistic complication caused by the intermediacy of *transoid* biradicals in the thermal reactions of vinylcyclopropanes. They reasoned that attachment of a *t*-butyl group to the vinyl side chain, as shown in Figure 25, would sterically disfavor the conformation of the reactant that would tend to give a transoid biradical. Apparently this strategy was successful because they found a diene:cyclopentene ratio of 2.38:1 (for the unlabeled compound at 280.0°C) instead of the more normal 11–16:1.

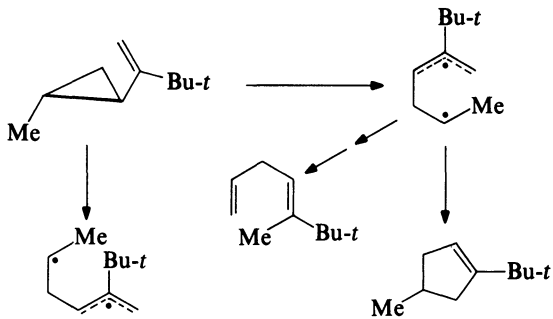


FIGURE 25

Having established that their vinylcyclopropane underwent reaction largely via a cisoid conformation, Gajewski and Warner went on to investigate isotope effects on the product ratio. They found that double deuteration of the terminal carbon of the vinyl group caused a decrease in the rate constant for cyclopentene formation by a factor of 1.125 ± 0.04. This normal isotope effect is not expected for a process in which sp^2 carbon is converted to sp^3 carbon in a single step (as would be the case for a concerted [1,3]sigmatropic shift mechanism). It would not usually be expected for rate-determining biradical formation either since this would not be expected to substantially change the hybridization at the labeled carbon. However, this reaction is special: the biradical, once formed, has a choice of (at least) two reactions, one leading to the cyclopentene and (at least) one leading to the diene. It is thus susceptible to an 'induced kinetic isotope effect'[58] in which an isotope effect on the partitioning ratio can appear in the rate constant for overall reaction even though the product-forming steps occur after the rate-determining step. In the present case, the biradical might be susceptible to a 'rotational isotope effect'[59] which would disfavor cyclopentene formation for the deuterated compound. Diene formation would consequently be favored, leading to the expectation of an inverse isotope effect for this branch of the reaction. This was observed, the value being $1/(1.11 \pm 0.04)$.

When the reaction was run with optically active starting material, it was found that interconversion of enantiomers of the reactant occurred without any measurable isotope

effect, as expected from the above analysis. Of somewhat greater surprise was the finding that this process occurred nearly twice as fast as the combined rearrangement reactions. This seems to rule out the possibility of rate-determining formation of a biradical that is common to the stereomutation and rearrangement processes. It is conceivable that the *t*-butyl group was not 100 % effective in preventing formation of transoid biradicals and that these are responsible for a large part of the racemization process. Alternatively, there is perhaps an explanation based on dynamic effects that will be discussed more in Section III.C.5.

Also somewhat surprising was the discovery that this reaction occurred with much lower stereoselectivity and with the opposite overall stereochemistry (net retention at the migrating carbon) from the system studied by Baldwin (Section III.C.1). The explanation for these differences does not seem immediately obvious[57].

4. Bicyclo[3.1.0]hexene and related compounds

The first reported study of the degenerate vinylcyclopropane rearrangement in a bicyclo[3.1.0]hexene ring was that of Doering and Lambert on the racemization and deuterium scrambling in α-thujene[60] (see Figure 26). They found that label scrambling and racemization occurred with rate constants that were equal within experimental error, a result consistent with the intermediacy of a biradical possessing a plane of symmetry (ignoring the isotopic label) that bisected the ring and reflected one methyl of the isopropyl group into the other (Figure 27). This experiment did not allow any conclusions to be drawn about the equilibrium geometry of the ring, in particular whether it was planar or whether it was puckered into a half chair geometry with the carbon bearing the isopropyl

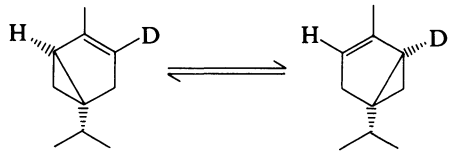


FIGURE 26

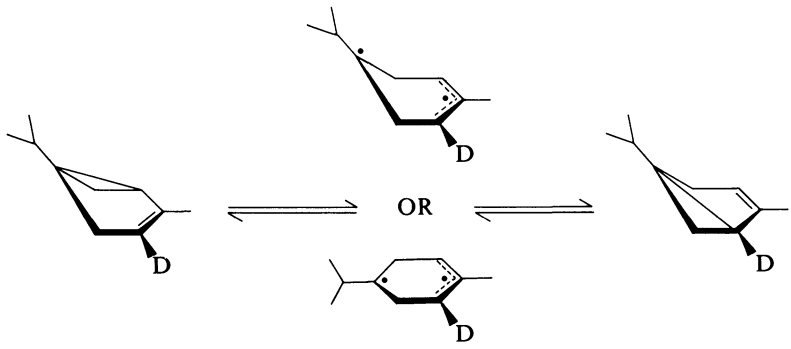


FIGURE 27

group being out of the plane of the other five ring carbons. This information could be garnered, however, from a study of rearrangement of α-thujene-2,2,3-d_3 (the terpene numbering system does not conform to IUPAC conventions) that involved resolution of a reaction taken to partial completion[61]. Such an experiment could, in principle, have been conducted equally well on the singly labeled α-thujene but the extra two labels facilitated NMR analysis of the deuterium distribution in the isolated enantiomers.

The results of this study are summarized in Figure 28. It was found that the results were not consistent with a biradical possessing a planar six-membered ring. Rather, they suggested the intermediacy of a puckered biradical that could undergo ring closure and recemization at comparable rates.

The later study of Cooke and Andrews[62] on the parent bicyclo[3.1.0]hexene did not fully concur with the conclusions of Doering and coworkers. The racemization of optically active bicyclo[3.1.0]hex-2-ene-2,4,4-d_3 was found to occur 1.33 ± 0.15 times faster than scrambling of the deuterium. Furthermore, the mechanistic quadrisection that Doering and Schmidt[61] had achieved by resolution of optically active compounds, was in this case studied by introduction of a single stereospecific deuterium label on C(4) (see Figure 29).

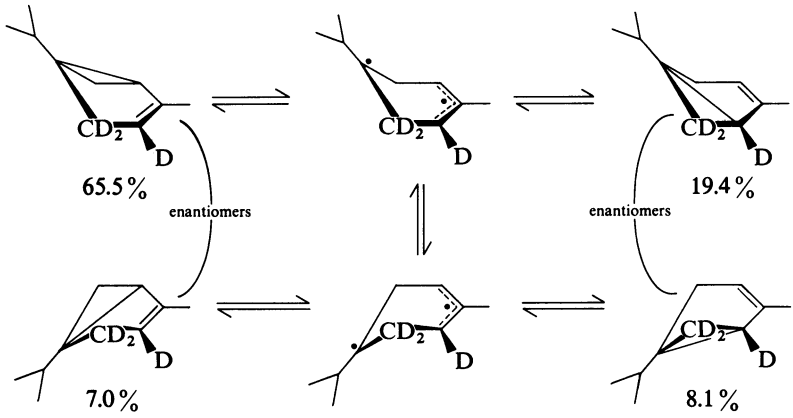


FIGURE 28

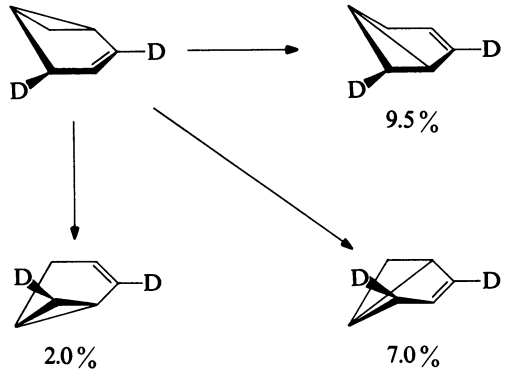


FIGURE 29

The outcome was again somewhat different from the Doering and Schmidt result. The major new isomer from a reaction run to approximately 25 % completion was found to be the one from rearrangement without ring flip in the putative puckered biradical (see Figure 29), as found by Doering and Schmidt. However the two minor products which, according to the biradical mechanism, should have been formed in a ratio differing from unity only by the amount of a secondary isotope effect were actually formed in a ratio of 3.5:1.

It is conceivable that the difference in the Doering and Cooke results can be attributed to the isopropyl group in α-thujene which would make the non-allylic radical center tertiary in the proposed intermediate. In the Cooke and Andrews' work the corresponding radical center would be secondary. Possibly the difference is enough to make the biradical longer lived and better able to achieve geometrical equilibrium in the experiments of Doering and coworkers. Whether the stereochemistry observed by Cooke and Andrews is the result of involvement of one or more pericyclic processes or whether it reflects dynamic phenomena in the biradical (see next section) is an open question.

5. *Bicyclo[2.1.1]hexene-5-d and related compounds*

Bicyclo[2.1.1]hexene was reported by Bond and Scerbo[63] to rearrange to bicyclo[3.1.0]hexene at about 180°C. Frey and coworkers[64] found the activation parameters to be $\log A = 13.95$, $E_a = 35.17$ kcal mol^{-1}. Roth and Friedrich[65] studied the stereochemistry of the reaction with *exo*- and *endo*-5-methyl derivatives. They found it to occur with preferential inversion of configuration at the migrating carbon, as anticipated for an allowed pericyclic [1,3]sigmatropic migration. However, the preference for inversion was not complete and substantial participation from a process occurring with retention could be detected when the inversion transition state was sterically disfavored.

The reaction is included in this chapter because recent work by Newman-Evans and Carpenter[66] has allowed the rearrangement of a number of deuterated analogues to be studied, and the products of these reactions are labeled cyclopropanes. It is included in this section because it is nominally a retro-vinylcyclopropane rearrangement.

The reactions studied are summarized in Figure 30 and the quantitative results in Table 1.

For each of the three bicyclo[2.1.1]hexenes predominant inversion of configuration was found, in agreement with the results of Roth and Friedrich. The stereoselectivity was found to decrease with increasing temperature for the parent system, in accord with the expectations for a competition between a highly stereoselective (presumably pericyclic) pathways and a higher energy, less stereoselective (possibly biradical) pathway. Much more startling was the discovery that the stereoselectivity of rearrangement for the two phenyl-substituted compounds was temperature independent within experimental error. If one wished to invoke the existence of competitive mechanism for rearrangement of these compounds, it would require an incredible coincidence in which the activation energies were identical to within a few tens of calories. The authors concluded that such a coincidence would be highly improbable for one compound and near impossible for two. If one accepts this analysis, then it becomes necessary to postulate the existence of a common intermediate (presumably a biradical) for the processes occurring with inversion and retention. But there are problems with this proposal, too. If the biradical were geometrically equilibrated it would give the products of inversion and retention in equal amounts. If it were not geometrically equilibrated and subject to the 'Principle of Least Nuclear Motion'[67] then it should afford more of the product corresponding to retention of configuration. Finally, if there were some kind of barrier favoring closure of the biradical with inversion of configuration, the product ratio should be temperature dependent. None of these expectations is in accord with the actual experimental results!

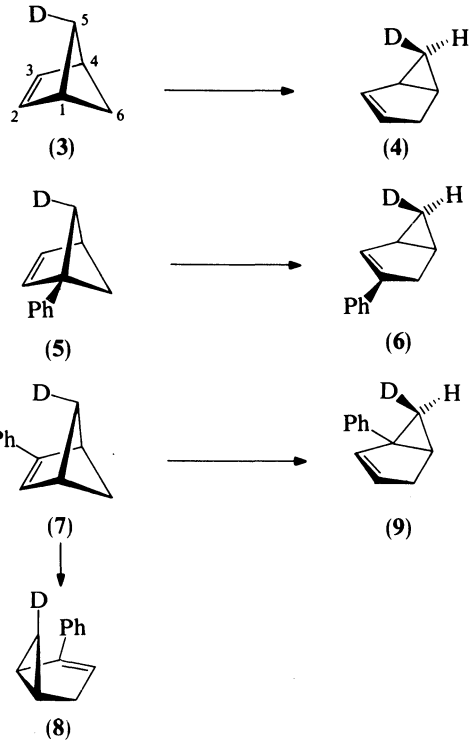


FIGURE 30

TABLE 1. Data on rearrangements of compounds **3**, **5** and **7**

Reaction	$\Delta H^{\ddagger a}$ kcal mol^{-1}	$\Delta S^{\ddagger a}$ cal mol^{-1} K^{-1}	KIE[b]	Stereoselectivity T(°C)	% Retention
3 → 4	34.8 ± 0.3[c]	3.9 ± 0.6[c]	1.07 ± 0.03	135.2	1.9 ± 0.4
				165.7	2.7 ± 0.3
				197.0	6.9 ± 0.5
5 → 6	28.9 ± 0.2[d]	0.0 ± 0.6[d]	1.25 ± 0.05	80.0	9.1 ± 0.3
				110.5	9.3 ± 0.4
				140.6	9.2 ± 0.4
				165.7	8.8 ± 0.3
7 → 8	35.7 ± 0.3[e]	1.6 ± 0.6[e]	*f*	*f*	
7 → 9	32.7 ± 0.2[e]	0.0 ± 0.5[e]	1.26 ± 0.05	124.9	12.1 ± 0.3
				144.6	11.7 ± 0.6
				160.2	12.7 ± 0.7
				181.3	11.7 ± 0.3

[a] Determined from unlabeled compounds.
[b] Ratio of unlabeled to labeled bridge migration.
[c] Rate constants measured at six temperatures from 130.1 to 175.3°C.
[d] Rate constants measured at seven temperatures from 82.6 to 133.5°C.
[e] Rate constants measured at seven temperatures from 130.1 to 181.3°C.
[f] Insufficient material to make the measurements.

A proposal that would explain the experimental results has recently been put forward[68]. It is perhaps somewhat controversial in that it implies that, at least for this reaction, Transition State Theory is incorrect. The idea can best be appreciated by reference to Figure 31. Calculations show that trajectories across this surface tend, because of the phenomenon of conservation of momentum, to take one from a reactant to the diagonally related product (i.e. **A** to **B′** or **A′** to **B**), corresponding to inversion of configuration. In words, as the bond to the CHD carbon is broken the configuration at that center goes from pyramidal to planar, but the momentum of this motion is conserved in the intermediate, leading to inversion of configuration as the preferred mode of product formation. The product ratio is determined by the Boltzmann weighting of the various trajectories (more specifically their total energy) which will of course lead to some temperature dependence. However calculations suggest that a typical experimentally accessible temperature range will not be large enough to cause a detectable change in product ratio.

It is interesting to note that if a similar phenomenon were to apply to cyclopropane stereomutation, one would expect inversion of configuration at both ends of the breaking C–C bond giving a stereochemistry in accord with the observations for cyclopropane-1,2-d_2 (Section III.A.3). Stabilization of the trimethylene biradical might place it in a potential

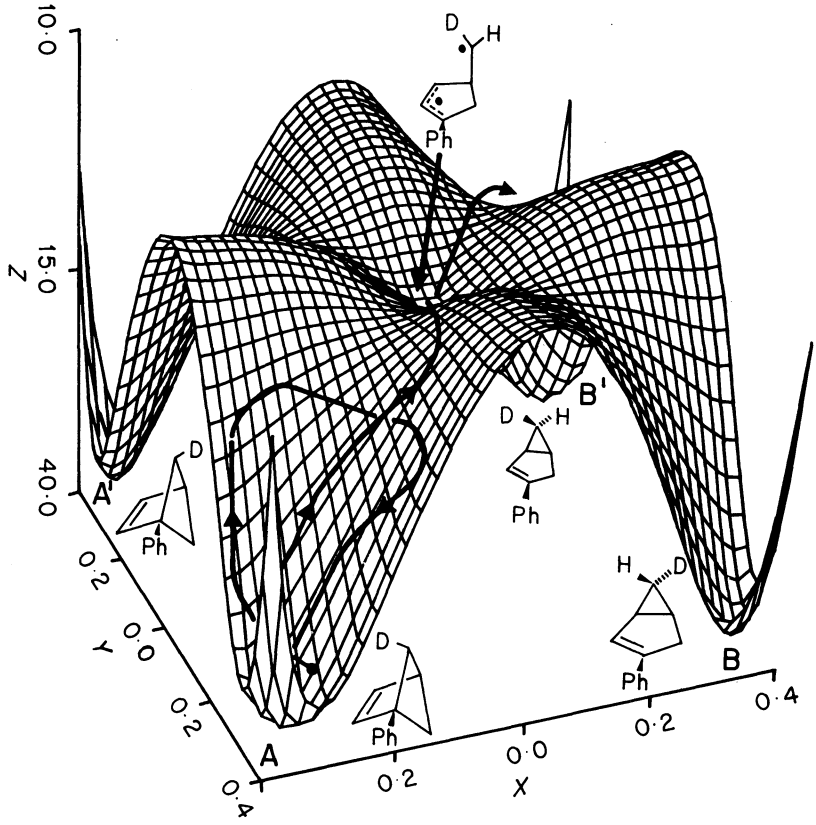


FIGURE 31

energy well that was sufficiently deep that trajectories would get 'lost' in the center and the momentum information would be lost as well. The upshot would be apparent uncorrelated or random stereochemical changes at the termini of the biradical, as expected for a Benson biradical (Section III.A.1).

Dynamic phenomena of this type might play a role in the vinylcyclopropane rearrangement, and would, for example, explain the apparent excess double inversion seen by Gajewski and Warner[57] (Section III.C.3) in the racemization of (*R,R*)-*trans*-2-methyl-1-(3,3-dimethyl-1-buten-1,1-d_2-2-yl) cyclopropane, without the need to postulate separate mechanisms for stereomutation and rearrangement. There is also some evidence for incursion of dynamic effects in the deazetization of pyrazolines (Section III.G).

D. Thermal Reactions of Labeled Cyclopropenes

Although a large amount of synthetic and mechanistic work has been done with cyclopropenes relatively little seems to have involved isotopically labeled compounds. This section describes some representative examples.

1. Methanolysis of tetrachlorocyclopropene

Tetrachlorocyclopropene reacts with sodium methoxide in methanol to give 2-chloro-1,3,3,3-tetramethoxypropene 1,2-dichloro-3,3,3-trimethoxypropene and 1-chloro-3,3,3-trimethoxypropyne (Figure 32). Work by Boberg and coworkers[69] using specific ^{14}C- and ^{36}Cl-labeled derivatives showed that the isotopic labels were statistically distributed in the products. The authors interpreted this result to mean that the trichlorocyclopropenium ion was an intermediate in the reaction.

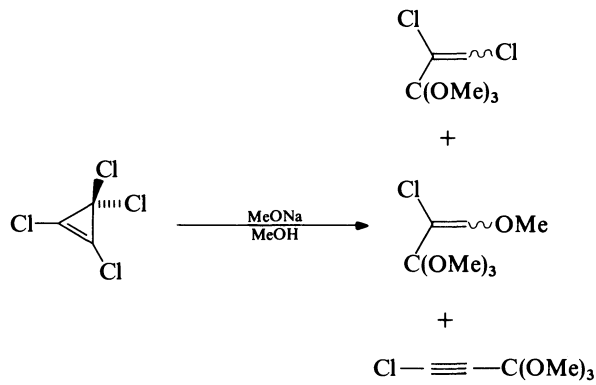


FIGURE 32

2. Cyclopropene as an intermediate in the propyne–allene interconversion

Pyrolysis of propyne at 500–750°C causes reversible conversion to allene. This process could, in principle, be a direct [1,3]sigmatropic hydrogen shift although the transition state for such a process, with simultaneous bonding of the migrating hydrogen to C(1) and C(3), is a little hard to visualize. Alternatively, as first suggested by Walsh[70a], the reaction could involve cyclopropene as an intermediate. The mechanisms can be distinguished by deuterium labeling: the direct [1, 3] shift starting with propyne-1-d can produce propyne-3-d only *after* formation of allene-d. The cyclopropene mechanism, on the other hand, can

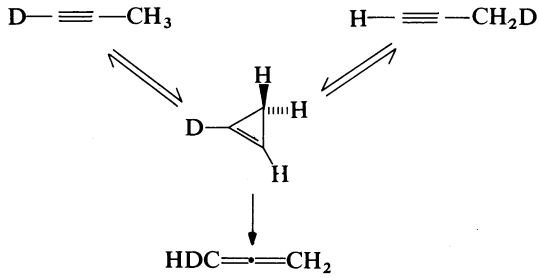


FIGURE 33

produce propyne-3-d *before* allene-d by reversible ring cleavage (see Figure 33). In the event[70b], the rate constant for conversion of propyne-1-d to propyne-3-d was found to be 3.5 ± 0.5 times greater than that for conversion of propyne-1-d to allene-d at 600–740°C. This result is consistent with the intermediacy of cyclopropene but not with the direct [1,3]hydrogen migration.

3. Allylic rearrangement in the decarbonylation of (2-cyclopropene-1-carbonyl)rhenium compounds

An elegant and interesting study using labeled cyclopropenes can be found in the work of Desrosiers and Hughes[71] on an organometallic decarbonylation reaction.

The migratory insertion reaction and its microscopic reverse are among the most common elementary processes in transition metal organometallic chemistry (see Figure 34). It had been thought that the topology of the reaction was always of the type that would be classified as a [1,2]sigmatropic migration in the terminology of organic pericyclic reactions; however, Desrosiers and Hughes showed that, in at least one case, the topology can be of the [2,3]sigmatropic type. Thus, **10** (Figure 35) was found to undergo thermal decarbonylation to **11** followed by a reverse migratory insertion to give **12**. The deuterium label was found to be exclusively at C(3) in the final product, indicating that the migration had occurred with allylic rearrangement, i.e. a [2,3]sigmatropic process.

E. The Methylenecyclopropane Rearrangement

1. Formulation of the problem

In 1932 Kon and Naji[72] reported that pyrolysis of *trans*-2,3-ethoxycarbonylmethylenecyclopropane ('Feist's ester') resulted in an isomerization to give compounds later identified[73] as the stereoisomeric 2-carbethoxy-1-(carbethoxymethylene)cyclopropanes (Figure 36). Subsequent studies by Ullman[74] using the optically resolved reactant showed that the products were not racemic and that the planar trimethylenemethane biradical could not, therefore, be the sole intermediate in the

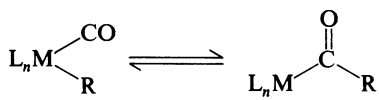


FIGURE 34

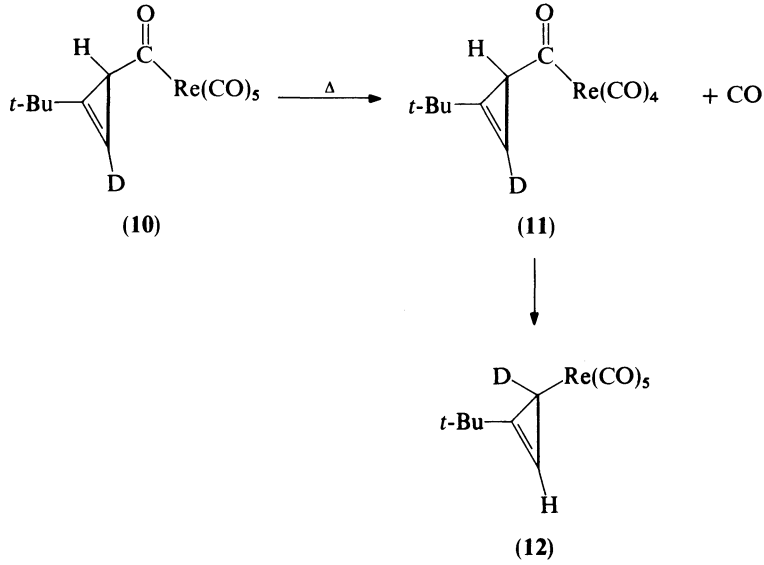


FIGURE 35

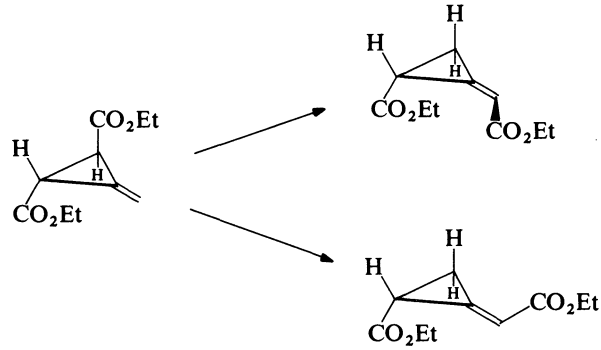


FIGURE 36

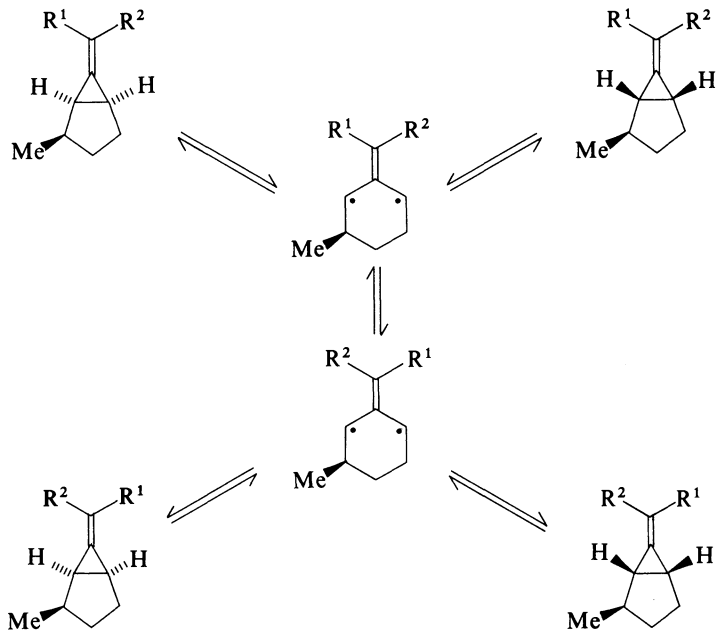
reaction (barring dynamic effects of the type proposed in Section III.C.5). Subsequent more detailed studies[75], discussion of which would be inappropriate for this chapter, have supported and expanded this conclusion. The contributions to the picture from studies involving isotopically labeled methylene cyclopropanes have been substantial and will be detailed below.

One reaction, mentioned in this section, combines some features of the methylenecyclopropane rearrangement and the vinylcyclopropane rearrangement (Section III.C): it is the pyrolysis of 2-vinyl methylenecyclopropane. Here, too, studies with deuterium-labeled compounds have been valuable in helping to unravel the various mechanistic pathways involved.

In addition to the thermal unimolecular rearrangement of methylenecyclopropanes, the reaction of these compounds with transition metal complexes has been investigated, in part through the use of specifically deuterated analogues. This, too, will be described in more detail below.

2. *Deuterium kinetic isotope effects on the thermal rearrangement of methylenecyclopropanes*

In 1977 Gajewski and Chou[76] reported a study of isotope effects on the rearrangements of 2,3-dimethylmethylenecyclopropane and 2-methyl-6-methylenebicyclo[3.1.0]hexane. When the exocyclic methylene was doubly deuterated for each of these compounds, kinetic isotope effects of 1.31 ± 0.04 and 1.08 ± 0.02, respectively, were found. The larger value was interpreted as a 'rotational isotope effect' caused by rotation of the exocyclic methylene in concert with the ring-opening process. The smaller value for the bicyclic compound was considered to be consistent with a mechanism in which initial ring-opening gave the planar biradical and rotation interchanging the locations of R^1 and R^2 then occurred in a subsequent fast step that was competitive with ring-closure (Figure 37). This mechanism for the rearrangement of the bicyclic compound was consistent with earlier results from Roth and Wegener[77] showing that *exo–endo* epimerization of optically active 3-methyl-6-ethylidenebicyclo[3.1.0]hexane occurred without complete racemization, apparently requiring some intervention from the locally planar biradical.



$R^1, R^2 = H,D$

FIGURE 37

3. *Formation and rearrangement of 2-methoxy-5-(methylene-d)bicyclo[2.1.0]pentane*

Clear-cut support for the Gajewski–Chou mechanism of rearrangement of bicyclic methylenecyclopropanes came from the study of formation and rearrangement of 2-methoxy-5-(methylene-d)bicyclo[2.1.0]pentane by the Berson group[78]. They showed that photochemical generation of the epimeric title compounds from an azo precursor (Figure 38) occurred without complete loss of stereochemistry at the labeled carbon. Of greater significance to the present discussion was the finding that conversion of the *endo* epimer to the *exo* occurred at −60°C, without scrambling of the deuterium, and that rotation of the exocyclic methylene occurred at a reasonable rate only at −40 °C. Finally, at temperatures in excess of 5 °C dimerization took place, thereby bringing together for the first time two apparently disparate aspects of methylenecyclopropane chemistry: stereomutation and trimethylenemethane dimerization.

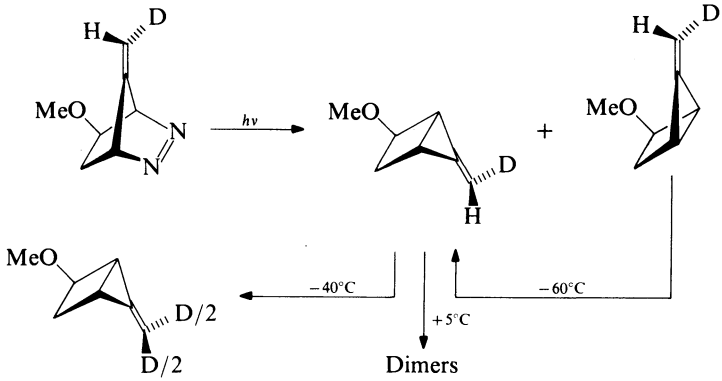


FIGURE 38

4. *Pyrolysis of 1-(methylene-d_2)-2-(vinyl-d_3) cyclopropane*

2-Vinyl methylenecyclopropane rearranges to 3-methylenecyclopentene with an activation energy of 25.8 kcal mol^{-1}. This is a ring expansion that is related to the vinylcyclopropane rearrangement (Section III.C) but occurs with an activation energy that is some 24 kcal mol^{-1} lower. In addition, deuterium labeling reveals that there is more going on. Gilbert and Higley[79] prepared and pyrolyzed the title compound. They found that there was a methylenecyclopropane rearrangement (degenerate but for the labels) occurring about ten times faster than the ring expansion. The two label-isomeric methylenecyclopentenes were formed in a near 1 : 1 ratio but there was a small (apparently statistically significant) time dependence of their ratio. The authors interpreted their data to mean that the major pathway involved an orthogonal biradical, common to the methylenecyclopropane rearrangement and the ring expansion (see Figure 39), with competition from a minor pathway that might be a concerted pericyclic process.

5. *Reaction of 2-phenyl-, 2,2-diphenyl- and* trans-*2,3-diphenylmethylenecyclopropanes-3-d with iron carbonyl reagents*

Substituted methylenecyclopropanes react with diiron nonacarbonyl to give trimethylenemethane and 1,3-diene iron tricarbonyl complexes[80]. Theoretical analysis of the former

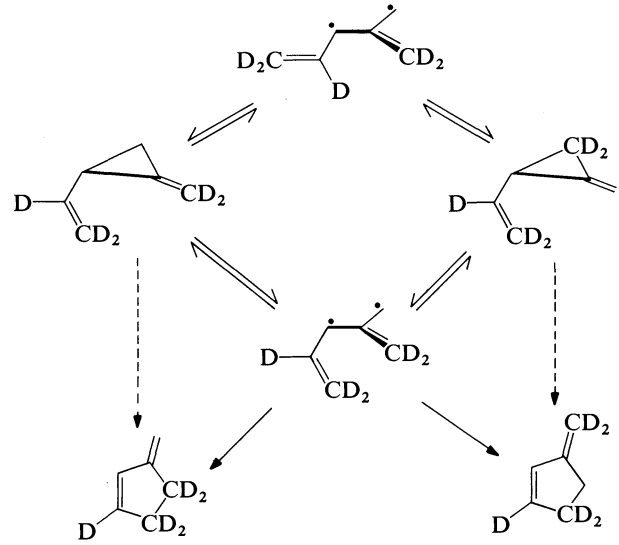


FIGURE 39

reaction indicated[81] that it might involve initial formation of a methylenecyclopropane iron tetracarbonyl complex followed by loss of carbon monoxide and ring-opening with a preferred stereochemistry that was disrotatory away from the metal (Figure 40). This prediction was confirmed in a series of experiments using stereospecifically deuterated, phenyl-substituted methylenecyclopropanes.

First, *cis*- and *trans*-2-phenylmethylenecyclopropanes-3-d were shown to give trimethylenemethane complexes with the deuterium at a location consistent only with disrotatory ring-opening[80e] (Figure 41). Second, reaction of 2,2-diphenylmethylenecyclopropane with a variety of iron carbonyl reagents allowed isolation of the methylenecyclopropane iron tetracarbonyl complex. This compound could be shown to give the trimethylenemethane complex on reaction with trimethylamine-*N*-oxide or diiron nonacarbonyl, both of which

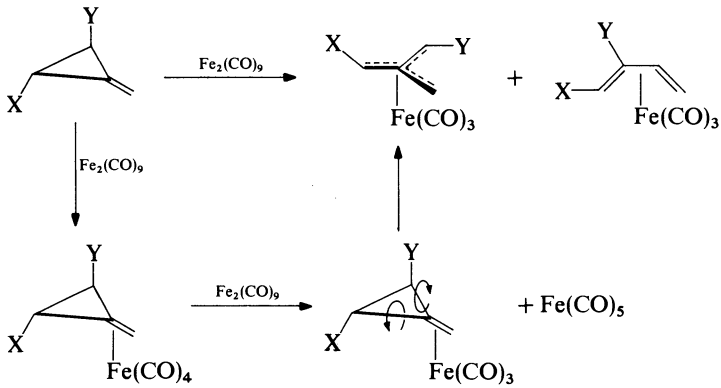


FIGURE 40

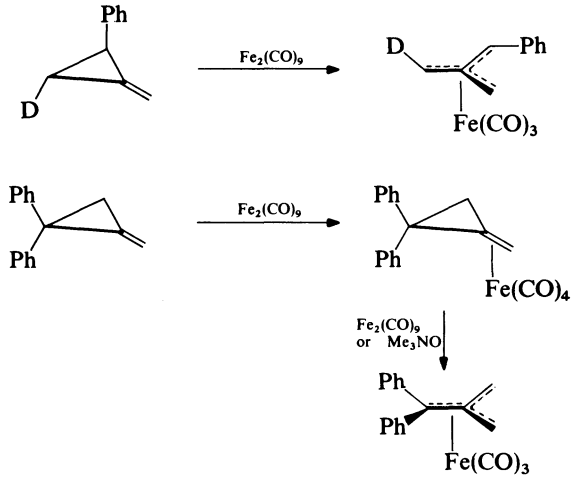


FIGURE 41

were thought to assist in decarbonylation[82]. Finally, detection of an 'induced kinetic isotope effect' on the product ratio from reaction of *trans*-2,3-diphenylmethylenecyclopropane-2-d with diiron nonacrbonyl could be shown to be consistent with a scheme in which the methylenecyclopropane iron tetracarbonyl complex was a common intermediate in formation of both trimethylenemethane and 1,3-diene complexes, the former being produced by the predicted disrotatory-away ring-opening[83]. 2,2-Diphenylmethylenecyclopropane-3-d was used in a control experiment in this final study.

F. Rearrangements of Labeled Bicyclo[6.1.0]nona-2,4,6-trienes

1. Thermal unimolecular rearrangement

Bicyclo[6.1.0]nona-2,4,6-triene (**13**, Figure 42) rearranges at 75°C to a 9 : 1 mixture of *cis*- and *trans*-8,9-dihydroindene (**14** and **15**)[84]. In addition, it undergoes a rapid epimerization at C(9), revealed by stereoselective deuterium labeling at that site[85]. On the other hand, deuterium labeling at C(3) and C(6) reveals no hydrogen migrations and no circumambulation of the cyclopropane ring[86]. Finally, bimolecular trapping experiments reveal that **13** is in rapid equilibrium with *cis,cis,trans,cis*-cyclonona-1,3,5,7-tetraene (**16**)[87]. When the trapping agent is tetracyanoethylene, present in large excess, the adduct formation shows first order kinetics with a rate constant identical to that for C(9) epimerization at the same temperature[88]. No evidence can be found for the intermediacy of *cis,cis,cis,trans*-cyclonona-1,3,5,7-tetraene (**17**) which would arise by direct conrotatory ring-opening of **13**[87c].

A scheme that would seem to be consistent with all of the facts is shown in Figure 43. Alternative routes to the all-*cis*-cyclonona-1,3,5,7-tetraene are possible but seem implausible. Thus competitive disrotatory ring-opening of either **13** or the bicyclo[5.2.0]nona-2,5,8-triene would provide pathways to the all-*cis*-cyclononatetraene but the activation parameters for these processes would have to be very unusual since it would be necessary to explain how they occur at negligible rates relative to the pathway shown in Figure 43 when the temperature is 31°C (where C(9) epimerization and trapping

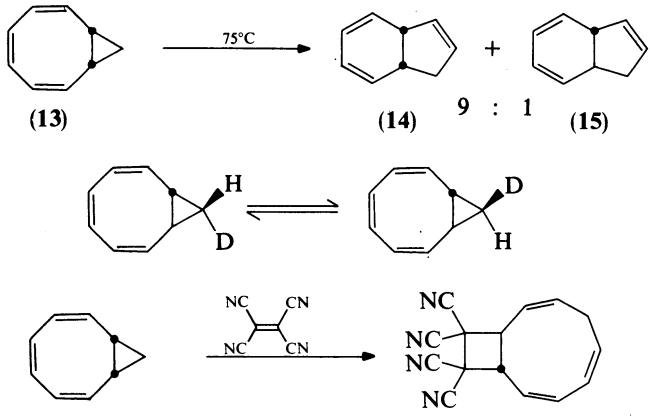


FIGURE 42

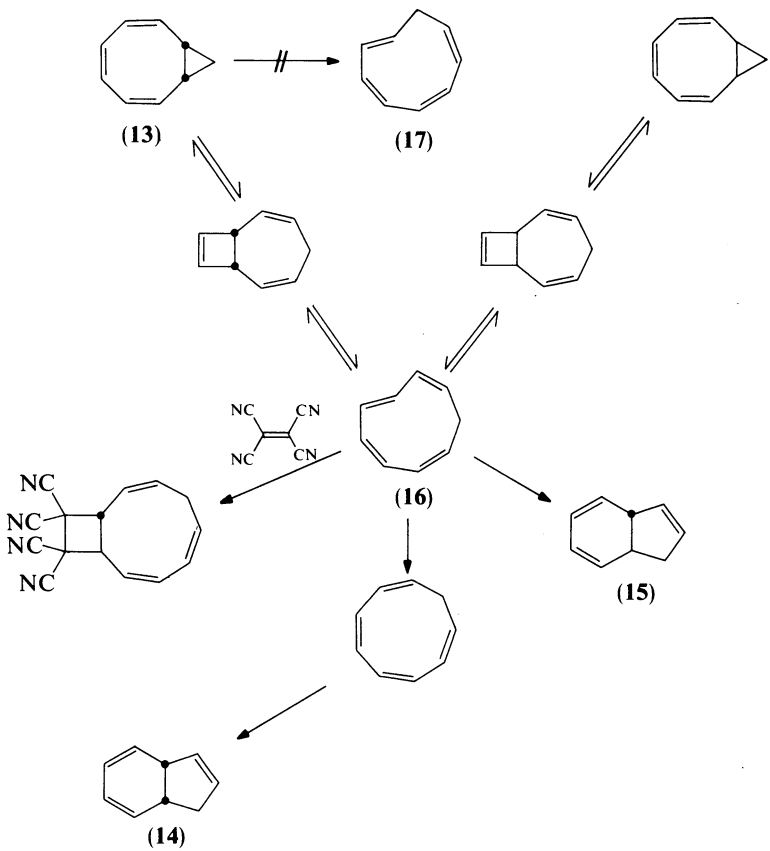


FIGURE 43

of specifically the *cis,cis,trans,cis* isomer have identical rate constants) but become dominant when the temperature is 75°C (where the rearrangement gives predominantly the *cis*-dihydroindene). Such a dramatic turnaround in relative rates would require a difference in $\Delta S^{\ddagger}$ of at least 60 cal mol^{-1} K^{-1} which, to say the least, seems unlikely.

G. Deuterium Isotope Effects on Pyrazoline Decomposition

As mentioned in the introduction to this chapter, 'uses' of labeled cyclopropanes has been interpreted rather liberally to include not only reactions in which a labeled cyclopropane is a reactant, but also those in which a labeled cyclopropane is an intermediate or a product. The pyrazoline pyrolyses belong to the last of these classes.

Thermal deazetization of pyrazolines results in the formation of cyclopropanes and alkenes[89], illustrated in Figure 44 for the parent compound (**18**). This reaction is of interest in that one could imagine that it would involve the same trimethylene biradical (**19**) proposed to be an intermediate in cyclopropane stereomutation (Section III.A). Supporting this notion is the observation that the parent pyrazoline gives 89% cyclopropane and 11% propylene at 250°C. If one took this product ratio as a reflection of the branching ratio from a common trimethylene intermediate, it should then be possible to compare these figures with the relative rates of stereomutation and propylene formation from cyclopropane-d_2[90]. Interestingly, they are identical.

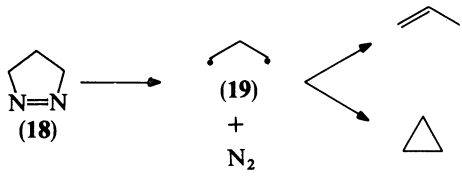


FIGURE 44

Despite this apparent similarity in the chemistry of cyclopropanes and pyrazolines, one might still be concerned that some of the products from pyrazoline pyrolysis could arise from a nitrogen-containing intermediate, such as a diazenyl biradical (**20**, Figure 45). This problem has been addressed by determination of isotope effects on pyrazoline decomposition. Al-Sader and Crawford[89e] have determined isotope effects for decomposition of the deuterated pyrazolines **21**–**24** at 230°C. The results are summarized in Figure 46. Of particular significance are the isotope effects for the α-deuterated compounds **21** and **22** which show the squared relationship expected for a symmetrical transition state[91], i.e. synchronous C–N bond cleavage without the intermediacy of a diazenyl biradical. The β-secondary isotope effects observed for **23** and **24** are unusually large for a non-solvolytic reaction and are perhaps consistent with a β effect being experienced simultaneously at two centers. The proposal of synchronous C–N bond

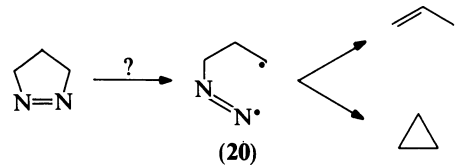
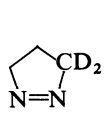
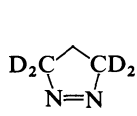


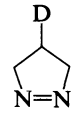
FIGURE 45



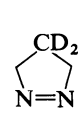
(21)



(22)



(23)



(24)

k_H/k_D	1.19	1.40	1.05	1.12

FIGURE 46

cleavage was supported by the work of Bergman and coworkers who studied isotope effects on the stereochemistry of cyclopropane formation from optically active, alkyl-substituted pyrazolines[92].

The question of a possible common intermediate in cyclopropane and alkene formation from pyrazoline deazetizations was addressed by Crawford and coworkers[89c] using 4-methylpyrazoline-4-d (Figure 47). They showed that introduction of the deuterium decreased the total rate of deazetization by a factor of 1.07 ± 0.03 at 250°C and changed the product ratio in favor of the cyclopropane by a factor of 1.80. In order for these results to be consistent with a process in which the pyrazoline gave cyclopropane and alkene by competitive unrelated steps, it would be necessary to postulate a β-secondary isotope effect on the cyclopropane formation of 1/2.62. First, this is an unprecedentedly large value for a secondary isotope effect, and, second, it is in the wrong direction. There is, at least to the knowledge of this author, no recorded case of an inverse β-secondary isotope effect. A much more plausible explanation of the data is that there is a single rate-determining step to give the trimethylene biradical that then partitions to give cyclopropane and alkene (Figure 48).

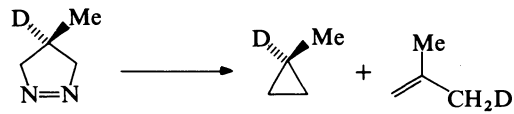


FIGURE 47

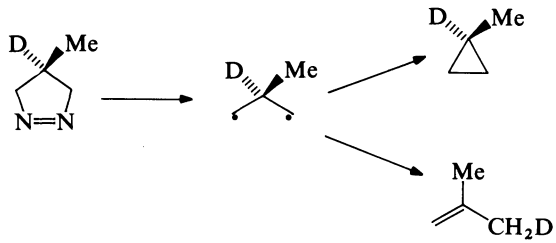


FIGURE 48

The stereochemistry of pyrazoline deazetizations is startling and, even now, difficult to understand. A case in point is the formation of bicyclo[2.1.0]pentane from 2,3-diazabicyclo[2.2.1]heptene. When the stereochemistry of the reaction is tested by introduction of labels at C(5) and C(6), it is found that product formation occurs with preferential inversion of configuration[93, 94] (Figure 49). Roth and Martin explained this in terms of backside displacement from a diazenyl biradical[93], but, as described above, the

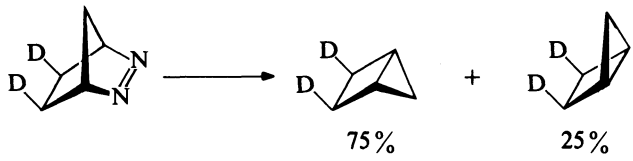


FIGURE 49

experimental data do not support the involvement of such an intermediate. Allred and Smith[94] interpreted the result as a 'recoil' effect caused by energy release associated with formation of N_2. Unfortunately this explanation has its own difficulties: Bauer has pointed out that in the deazetization of a pyrazoline by synchronous C–N bond stretching, the N=N stretching vibration would be orthogonal to the reaction coordinate[95]. Accordingly the molecular nitrogen would be formed with an internuclear distance far from its equilibrium value, corresponding to substantial vibrational excitation. Thus, by this analysis, the nitrogen should carry off more than the ergodic amount of vibrational energy, leaving the hydrocarbon fragment vibrationally cold—just the opposite of Allred and Smith's proposal. One possible explanation that does seem to fit the facts is that the deazetization reaction is subject to the dynamic effects discussed in Section III.C.5. The motion leading to planarization at C(1) and C(4) that occurs as the nitrogen departs is continued in the cyclopentane-1,3-diyl and leads to product with, most frequently, inversion of configuration at both centers.

Interestingly the inversion observed for 2,3-diazabicyclo[2.2.1]heptene is not found in the deazetization of its lower homologue, 2,3-diazabicyclo[2.1.1]hexene-5-*exo*-d[96] which gives bicyclo[1.1.0]butane-2-d with a 1:1 *exo*:*endo* distribution of the label. There is evidence, however, that the hydrocarbon product may be produced in a chemically activated form and so the final label distribution might be the result of secondary isomerization[96].

The stereochemistry of decomposition of monocyclic pyrazolines is more complicated still. It is not appropriate to discuss this work here since most of it was conducted on alkyl-substituted, unlabeled compounds, but the interested reader is referred to the paper by Bergman[92] for a thorough experimental study and a good review of earlier work.

IV. CATION REACTIONS

Two cationic structures, protonated cyclopropane and the cyclopropylcarbinyl cation, were among the earliest for which 'non-classical' structures were proposed. Structure elucidation for both of these reactive intermediates owes much to the use of labeled cyclopropanes; they will be the focus of attention in this section.

A. Protonated Cyclopropanes

Roberts[97] seems to have been the first to propose the existence of a carbonium ion intermediate with a bridging methyl group (a structure that we would now call a 'corner-protonated' cyclopropane), in part as a result of a study on the deamination of propylamine-1-^{14}C in an aqueous medium, in which it was believed that a small amount of label migration to both C(2) and C(3) of the 1-propanol product was observed (Figure 50). In fact, the analysis of the label position was later shown to be in error[98] but, by then, other experiments had suggested the existence of some kind of protonated cyclopropane. Among these were studies showing the formation of cyclopropanes from deamination of alkylamines in non-aqueous media[99]. This process was subjected to further scrutiny

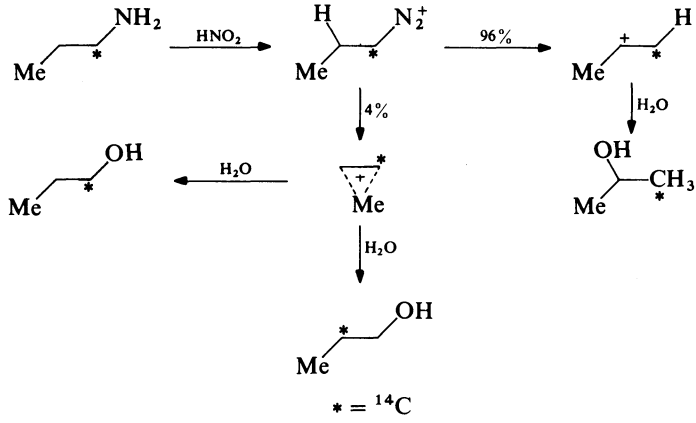


FIGURE 50

through the use of deuterium-labeled reactants, leading to the formation of deuterated cyclopropanes; thus 1-propylamine-3,3,3-d_3 was found to give a mixture of cyclopropane-d_3 and cyclopropane-d_2 in a ratio of (1.33 ± 0.05): 1 upon deamination[100]. This result was interpreted in terms of equilibration among 'edge-protonated' cyclopropanes with the 'corner-protonated' species serving as transition states for the hydrogen migrations (Figure 51). The data would be fit quantitatively if there was an isotope effect of 2.7–3.0 on the proton loss.

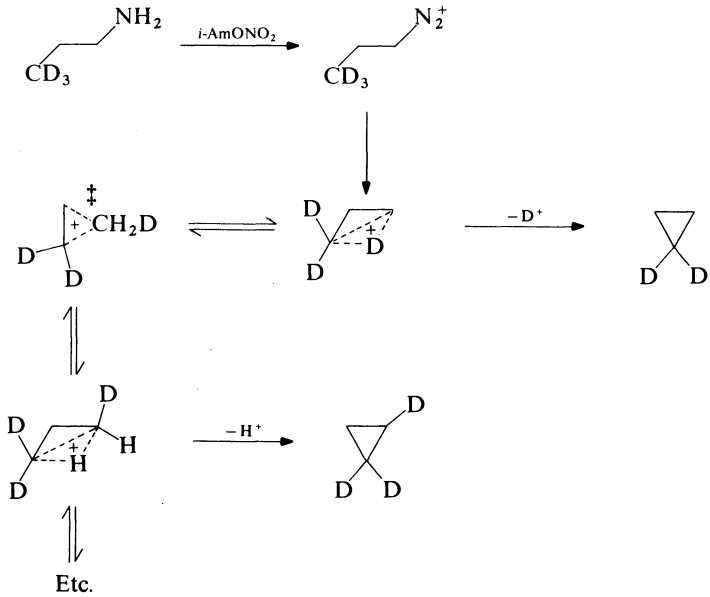


FIGURE 51

Further support for the intermediacy of edge-protonated cyclopropanes came from a study of the ring-opening of cyclopropane in 8.4 M deuteriosulfuric acid[101]. The reaction afforded 1-propanol-d with the label distribution being 38% at C(1), 17% at C(2) and 46% at C(3). This distribution is inconsistent with a process involving isomerization and trapping of corner-protonated cyclopropanes since one would then expect (barring an unprecedentedly large secondary isotope effect) to get approximately equal amounts of deuterium at C(1) and C(2). It is consistent with equilibrating edge-protonated cyclopropanes (as in Figure 52) provided that trapping of the ions is competitive with hydrogen migration.

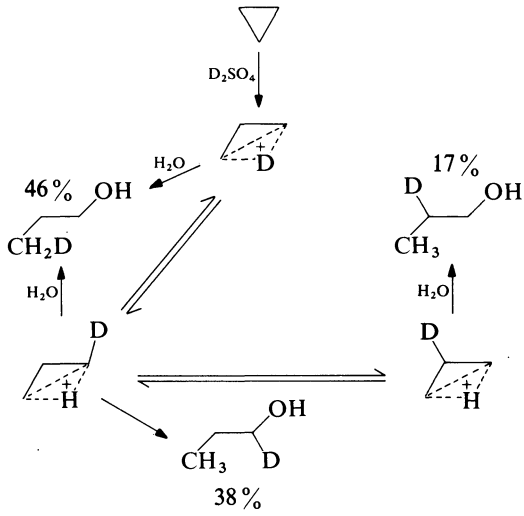


FIGURE 52

Despite these results appearing to favor the edge-protonated structure over the corner-protonated one, there was already in existence experimental evidence showing that the preference could not be a universal one for all cyclopropanes. Thus the now-infamous skeletal rearrangement of the 2-norbornyl cation[102] passes through a symmetrical structure (which may or may not be an intermediate!) that can be considered to be a corner-protonated cyclopropane (**A** in Figure 53). This reaction occurs faster than the 6,2-hydride shift for which the symmetrical structure is akin to an edge-protonated cyclopropane (**B** in Figure 53). The faster carbon migration shows that, at least in this case, the corner-protonated structure is more stable.

The preference for the edge-protonated structure emerges from interesting microwave spectroscopy experiments[103] conducted on the cyclopropane–hydrogen fluoride and cyclopropane–hydrogen chloride complexes which reveal a structure like that shown in Figure 54.

The apparent discrepancy in assignment of structure to the protonated cyclopropanes from the experiments described above could be resolved if corner-protonated and edge-protonated ions were in fact very close in energy and if the preference for one or other then depended on substituents. As it happens, this is exactly the picture that emerges from molecular orbital calculations on protonated cyclopropane. While early calculations seemed to favor the corner-protonated structure[104], later ones involving extensive electron

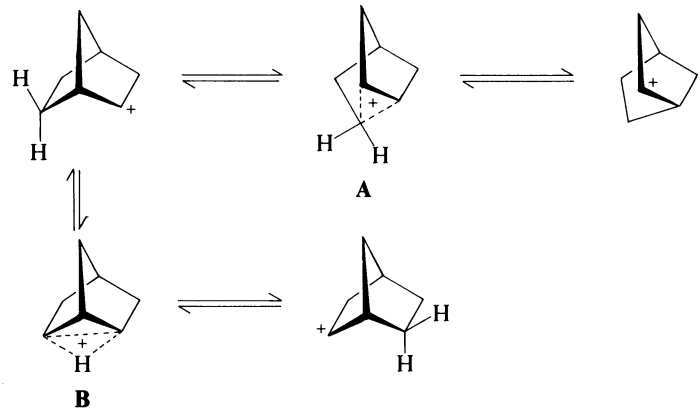
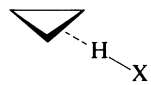


FIGURE 53



X = F, Cl

FIGURE 54

correlation corrections show them to be essentially isoenergetic[105]. The calculations of Wiberg and Kass[105b] further show that simple alkyl substitution causes dramatic changes in the calculated equilibrium geometries.

For strained bicyclic molecules such as bicyclo[2.1.0]pentane calculations suggest a strong preference for protonation at a bridgehead carbon[106]. This prediction seems to be consistent with experimental results[106] in which bicyclo[2.1.0]pentane-*endo*-5-d is solvolyzed in acetic acid containing *p*-toluenesulfonic acid to give cyclopentyl acetates and tosylates (as well as some cyclopentene) in which distribution of the deuterium among all possible sites could be quantified. Isotope effects and label distributions were found to be consistent with the initial formation of a C(1)-protonated bicyclo[2.1.0]pentane.

Protonation of bicyclo[1.1.0]butane at C(1) leads to an interesting structure that has been proposed as an intermediate in the solvolysis of cyclopropylcarbinyl and cyclobutyl compounds. It is the subject of the next section.

B. The Cyclopropylcarbinyl Cation

Deamination of cyclopropylmethylamine or cyclobutylamine in an aqueous medium results in the formation of essentially the same ratio of products[107] (Figure 55). These products are formed also from the solvolysis of homoallyl tosylate in a weakly nucleophilic medium such as 98% formic acid. It is tempting, then, to speculate that there could be a common mechanism linking the solvolyses of all three classes of substrate[108].

When cyclopropylmethylamine labeled at the nitrogen-bearing carbon with ^{14}C is deaminated, the label is found to be distributed almost equally among the three methylene groups in each of the products (Figure 56)[108a]. This result could be explained by rapid

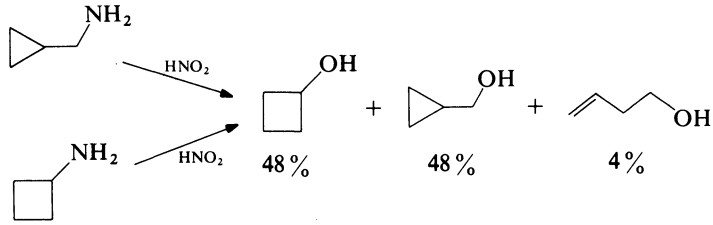


FIGURE 55

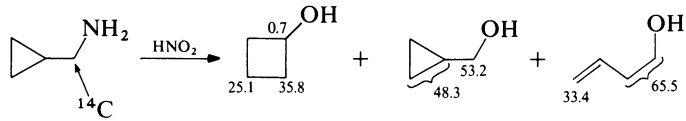


FIGURE 56

Wagner–Meerwein migrations within a cyclopropylcarbinyl cation (Figure 57). However there is another interesting fact about these reactions that led Roberts to suggest an alternative possibility: solvolysis of cyclopropylcarbinyl tosylate is about a million times faster than that of its nearest acyclic analog, isobutyl tosylate[109], suggesting that the cation produced from the former is especially stabilized. This fact and the observation of the facile equilibration of methylene groups led Roberts to propose that all three substrates led

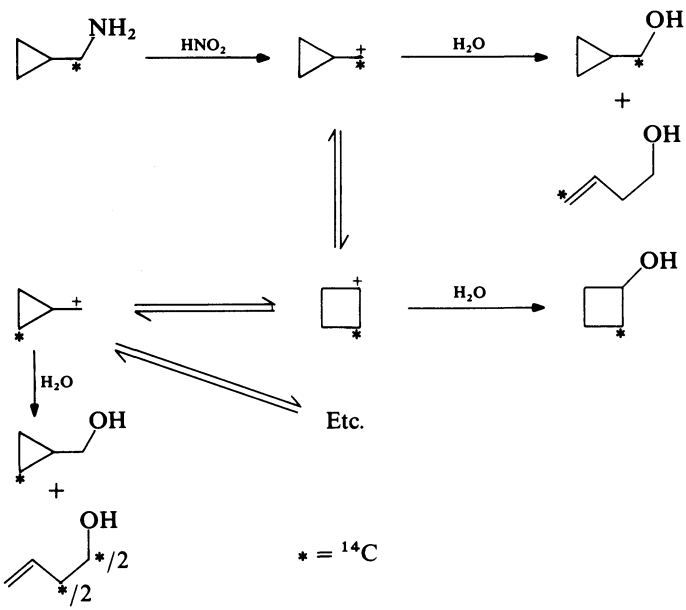


FIGURE 57

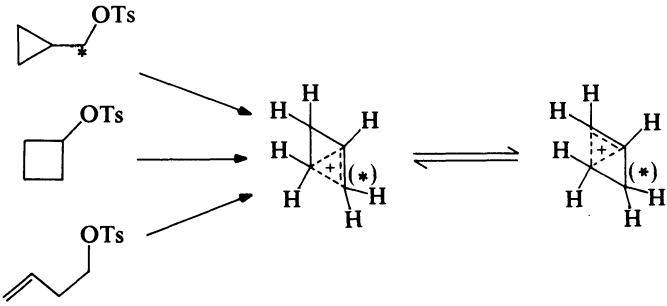


FIGURE 58

eventually to a non-classical 'bicyclobutonium' ion that could undergo degenerate rearrangements (Figure 58).

Considerable support for Roberts' suggestion has come from later studies, notably those involving NMR studies in superacid media. Thus, while the spectrum of the α,α-dimethylcyclopropylcarbinyl cation is best rationalized in terms of a classical structure[110], that for the parent system is consistent with neither static nor rapidly equilibrating classical structures[111]. The parent system seems best to be described as a mixture of the equilibrating bicyclobutonium ions and, less than 4 kcal mol^{-1} higher in energy another structure that might be the classical cyclopropylcarbinyl cation[111].

The α-methylcyclopropylcarbinyl cation is an interesting intermediate case. It seems to have the classical structure as its lowest energy geometry, but studies by Sorensen and coworkers[112] on the interconversion of *syn* and *anti* isomers suggest that the reaction, far from being a simple rotation, actually occurs by way of no fewer than *seven* intermediates! Included in these is the 1-ethylallyl cation which is directly observable in the reaction mixture. Supporting its intermediacy in the *syn–anti* interconversion is a deuterium-labeling study: 1-cyclopropylethanol-1-d is found to give α-deuterio-α-methyl-cyclopropylcarbinyl cation which then rearranges to the ring-labeled compound; the deuterium appears in both *cis* and *trans* positions at the same rate, consistent with the involvement of an intermediate in which these two sites are equivalent by symmetry (Figure 59).

The stereochemistry of rearrangement in the parent system was studied by Majerski and Schleyer[113] using a cyclopropylcarbinyl mesylate that was fully deuterated except for one

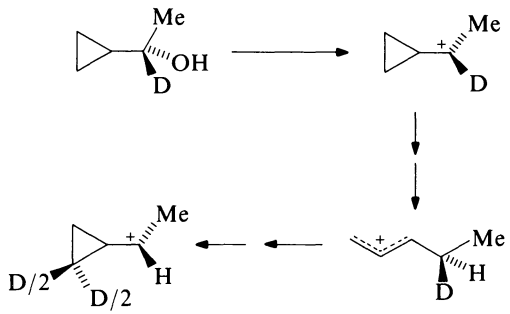


FIGURE 59

proton on the ring *cis* to the side chain. They concluded that all rearrangements were, within experimental error, completely stereospecific.

Theoretical studies[114] on the cyclopropylcarbinyl cation have suggested that the bicyclobutonium ion and the classical cyclopropylcarbinyl cation should be close in energy. The *ab initio* studies of Hehre and coworkers[115] give a small (0.5 kcal mol^{-1}) preference to the classical structure, but this is surely well within the confidence limits of the calculations. Dewar and Reynolds' more recent MINDO/3 calculations[116] give a 5.6 kcal mol^{-1} preference to a structure that they characterize as a 'cyclobutyl cation' but which, on inspection of the calculated geometry looks more like a C(1)-protonated bicyclo[1.1.0]butane. The structure of next highest energy is the classical cyclopropylcarbinyl cation. The C(1)-protonated bicyclo[1.1.0]butane has a geometry that is similar to that proposed by Roberts for his bicyclobutonium ion and thus serves as a conceptual bridge between the chemistry of protonated cyclopropanes and that of cyclopropylcarbinyl cations. In fact protolytic cleavage of bicyclo[1.1.0]butane does give the typical cyclopropylcarbinyl products[117]. When the reaction is carried out with deuterated acetic acid the cyclopropylcarbinyl acetate is found to have essentially all of the ring deuterium *cis* to the carbinyl carbon, indicating retention of configuration at the carbon to which the proton is added (Figure 60).

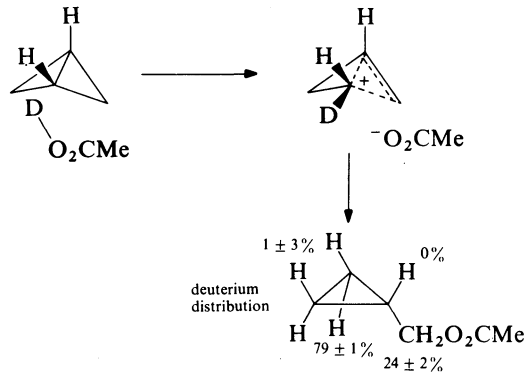


FIGURE 60

V. ANION REACTIONS

A. Cyclopropyl Anions

Most alkyl carbanions undergo facile pyramidal inversion. Cyclopropyl anions are an exception, presumably because the transition state, with a planar trigonal carbon, is more strained than the ground state. The configurational stability of cyclopropyl anions is of value in the synthesis of deuterated cyclopropanes by the Haller–Bauer reaction (see Section II.B). An interesting dilemma arises when a cyclopropyl anion is stabilized by a π-electron acceptor substituent such as a nitrile or an ester. Will the anion then retain its pyramidal equilibrium geometry for the strain reasons alluded to above, or will it become planar in order to maximize overlap of the filled orbital on carbon with the π^* orbital of the substituent? Walborsky and coworkers[118] addressed this question in a series of experiments in which rates of H/D exchange and racemization were compared for an optically active cyclopropane exposed to a base in a deuterated hydroxylic solvent. The outcome can be illustrated with the particular example of 1,1-diphenylcyclopropane-2-

carbonitrile (Figure 61). At 50°C in MeOD with MeONa as base the ratio of rate constants for racemization (k_α) and H/D exchange (k_{ex}) was found to be 1.24×10^{-4}. This is consistent only with a pyramidal ion that can undergo slow inversion.

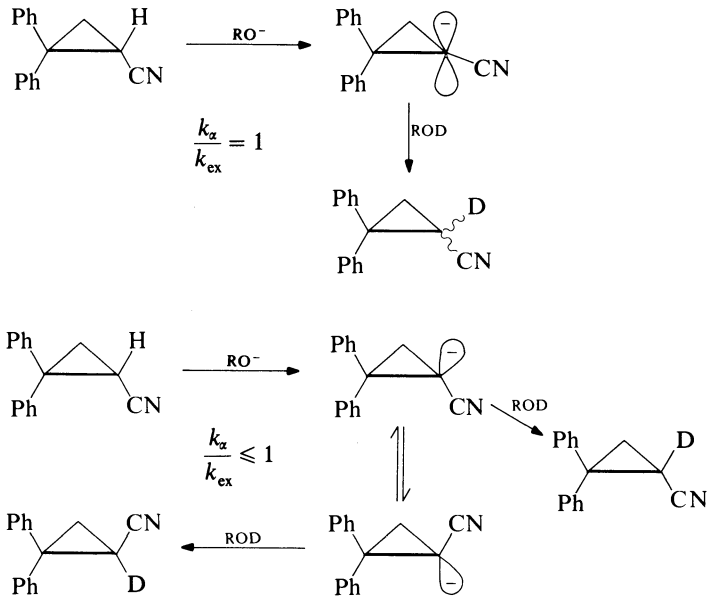
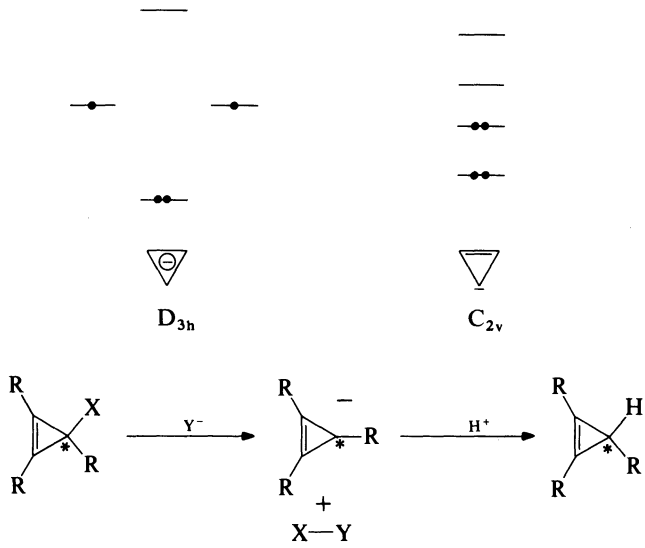


FIGURE 61

B. Triphenylcyclopropenyl Anion

The cyclopropenyl anion has 4 π electrons and is thus classified as antiaromatic. This means that the symmetrical (D_{3h}) structure should be unstable with respect to Jahn–Teller distortion, at least for the lowest singlet state. The most probable structure for the distorted ion is the C_{2v} geometry in which one of the ring carbons is distinguishable from the other two (Figure 62). If this analysis is correct and if the barrier to automerization is substantial, it should be possible to generate a cyclopropenyl anion from a cyclopropene that is labeled at C(3) and then trap the ion without label scrambling among the three ring carbons (Figure 62).

Borden and coworkers[119] tried this experiment with the triphenylcyclopropenyl anion (the phenyl groups were necessary to reduce the pK_a of the conjugate acid). The precursor was the 3-trimethylsilyl-1,2,3-triphenylcyclopropene-3-^{13}C, from which the anion was generated by treatment with tetra-*n*-butylammonium fluoride. The anion was protonated by adventitious water and the resulting triphenylcyclopropene analyzed by ^{1}H-NMR. The distribution of the label was within experimental error of the statistical value. If one accepts the validity of the Jahn–Teller theorem, this result implies either that the barrier to automerization is small or that there is a considerable contribution from carbon tunneling, as has been suggested for the analogous process in cyclobutadiene[120].



e.g. X = $(Me)_3Si$; Y = F; R = Ph

FIGURE 62

VI. RADICAL AND CARBENE REACTIONS

A. Cyclopropyl Radicals

In acyclic aliphatic systems carbanions tend to have a pyramidal equilibrium geometry whereas radicals are either planar (methyl and ethyl) or slightly pyramidalized with a very low barrier to inversion (*t*-butyl). The experiments of Walborsky and coworkers[118] (Section V.A) showed that in cyclopropyl carbanions the barrier to inversion of the pyramidal structure was substantially increased. By analogy, then, one might anticipate that cyclopropyl radicals would be pyramidal but with a lower barrier to inversion than for the anion. Experiments to test this idea were again conducted by Walborsky and Chen[121] (*inter alia*). They heated the optically active diacyl peroxide **25** (Figure 63) in a variety of solvents containing radical traps—a typical example being I_2 in CCl_4. The cyclopropyl iodide so produced was found to be racemic, indicating that the radical intermediate was either planar or rapidly inverting. The resolution came from examination of a minor product in the reaction: 1-methyl-2,2-diphenylcyclopropane (**26** in Figure 63). This compound was found to be about 34% optically pure (67% retention of configuration). The extra hydrogen was shown to be derived from disproportionation within a solvent cage by a double-labeling crossover experiment in which equimolar amounts of the d_0 and the d_{10} peroxide (labeled on the methyl group and cyclopropyl methylene of each ring) were mixed and pyrolyzed. The resulting 1-methyl-2,2-diphenylcyclopropane was found to be only d_0 and d_6 by mass spectrometry; none of the d_1 or d_5 material that would have arisen from disproportionation after cage escape could be detected (Figure 64). Thus the picture that emerges is of a cyclopropyl radical that is pyramidal and can react within the solvent cage at a rate comparable to the rate of inversion but which escapes from the cage at a rate considerably slower than the rate of inversion.

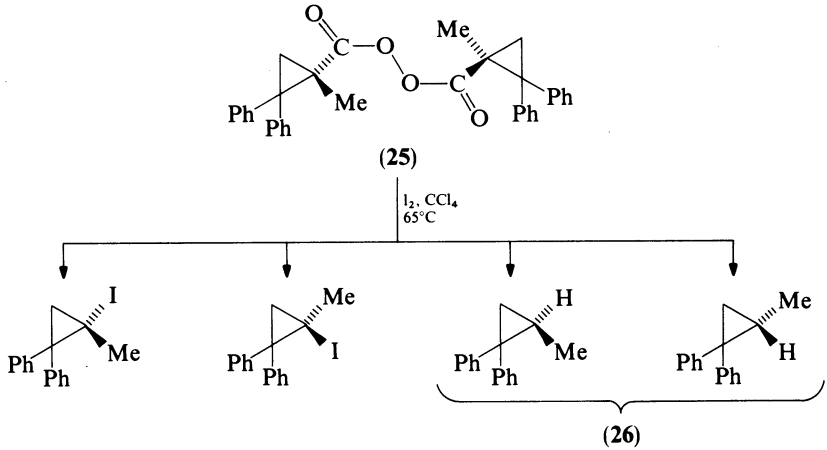


FIGURE 63

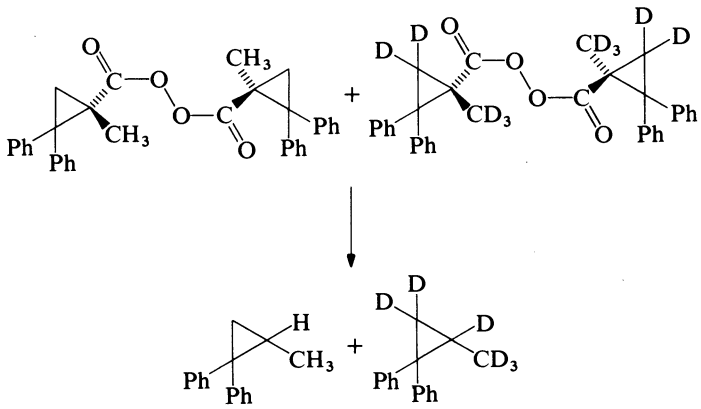


FIGURE 64

B. Cyclopropenylmethylene, Bicyclobutanylidene and Tetrahedrane

Tetrahedrane (tricyclo[1.1.0.$0^{2,4}$]butane) is a highly strained compound that has yet to be directly detected (although the tetra-*t*-butyl derivative has been isolated[122]). Nevertheless, some ingenious labeling experiments have suggested its intermediacy in certain carbene reactions.

The first of these was a study by Shevlin and Wolf[123] who showed that photochemical addition of carbon suboxide to cyclopropene resulted in the formation of vinyl acetylene and acetylene. They postulated the intermediacy of bicyclobutanylidene as a source of the former and tetrahedrane as a source of the latter (Figure 65). The postulated intermediacy of tetrahedrane was supported by two labeling studies. In the first cyclopropene-3,3-d_2 containing $87.1 \pm 3.2\%$ deuterium was used. The resulting acetylene was analyzed for

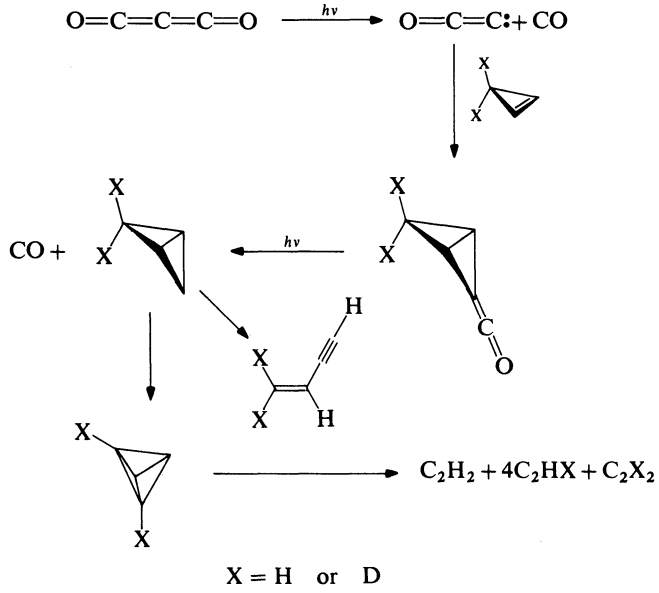


FIGURE 65

deuterium distribution and found to be very close to that predicted for a tetrahedrane intermediate (Table 2).

TABLE 2. Percent deuterium distribution in acetylene products

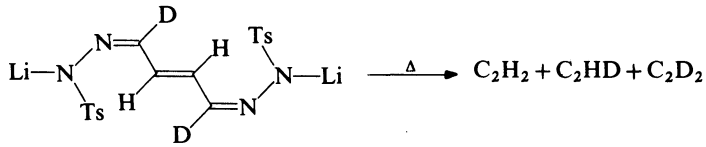
Acetylene	Observed	Calculated
C_2H_2	23.7 ± 2.5	25.0
C_2HD	63.6 ± 1.2	62.4
C_2D_2	12.8 ± 1.4	12.6

Then, in a second experiment, carbon suboxide labeled at the central atom with ^{14}C was photolyzed in the presence of cyclopropene-3,3-d_2. The resulting acetylenes were reduced to the corresponding ethylenes with chromous chloride and these were then separated on the basis of deuterium content by gas chromatography. The ^{14}C content of each ethylene was then analyzed and, again, found to be very close to that expected for a tetrahedrane intermediate (Table 3).

TABLE 3. Percent ^{14}C activity in acetylene products

	^{14}C Activity	
Acetylene	Observed	Calculated
C_2H_2	13.8 ± 5	12.9
C_2HD	59.4 ± 5	61.8
C_2D_2	26.8 ± 5	25.3

The second type of reaction in which a tetrahedrane intermediate could be implicated came from a study by Rodewald and Lee[124]. They pyrolyzed the bis(lithiotosylhydrazone) **27** (Figure 66), in which each labeled site contained 87% deuterium, and obtained 4.5 ± 0.2% C_2D_2, 77.7 ± 0.5% C_2HD and 17.8 ± 0.5% C_2H_2. This result showed that most of the acetylene was produced without scrambling, either by direct fragmentation from an acyclic precursor, or by fragmentation of a cyclopropenylmethylene (see Figure 67). However, some of the acetylene (37–47%, depending on the mechanism) had to arise after a scrambling process that seems to require the bicyclobutane-2,4-diyl and/or tetrahedrane.



(27)

FIGURE 66

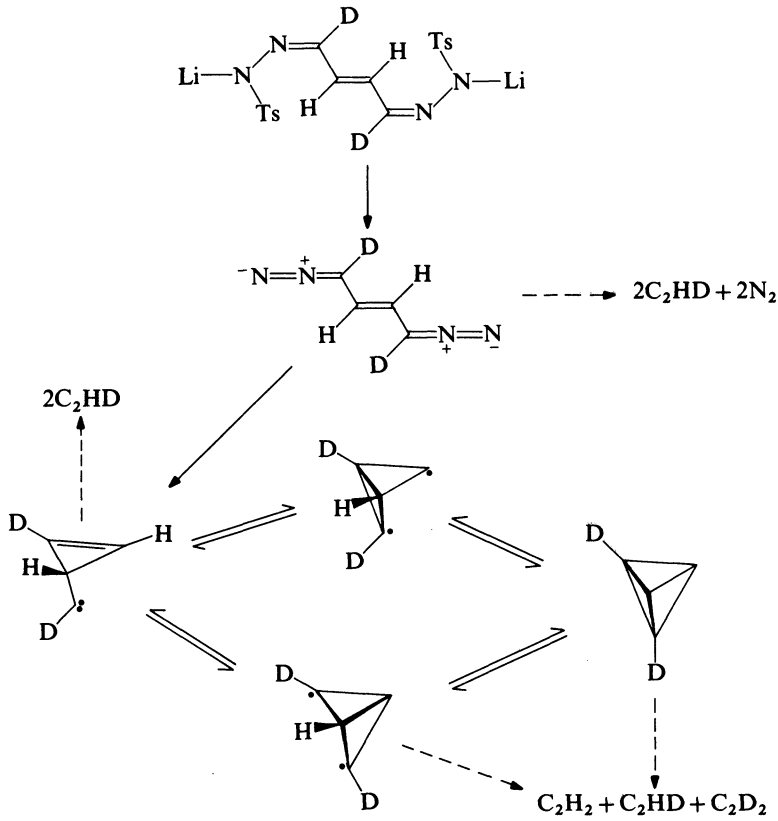


FIGURE 67

VII. PHOTOCHEMISTRY

A. Degenerate Rearrangement of Benzvalene

The photochemistry of benzene has been thoroughly studied. The lowest vibrational state of S_1 is fluorescent but apparently unreactive; a higher vibrational state of S_1 gives benzvalene (**28**, Figure 68) and thence, by inefficient secondary photochemistry, fulvene; S_2 gives Dewar benzene (**29**). In 1975 Katz and coworkers[125] studied the photochemistry of benzvalene-5,6-d_2 in order to elucidate more details of the processes involved. They found that the inefficiency of its conversion to fulvene was due to the occurrence of a facile degenerate rearrangement that was apparent only after introduction of the isotopic labels (Figure 69). The rearrangement occurred with direct photolysis, singlet sensitization, or triplet sensitization (provided that the triplet sensitizer had $53 < E_T < 65$ kcal mol^{-1}). Triplet sensitization with sensitizers having $E_T > 65$ kcal mol^{-1} gave benzene-1,2-d_2 in a quantum chain reaction with quantum yields approaching 4.

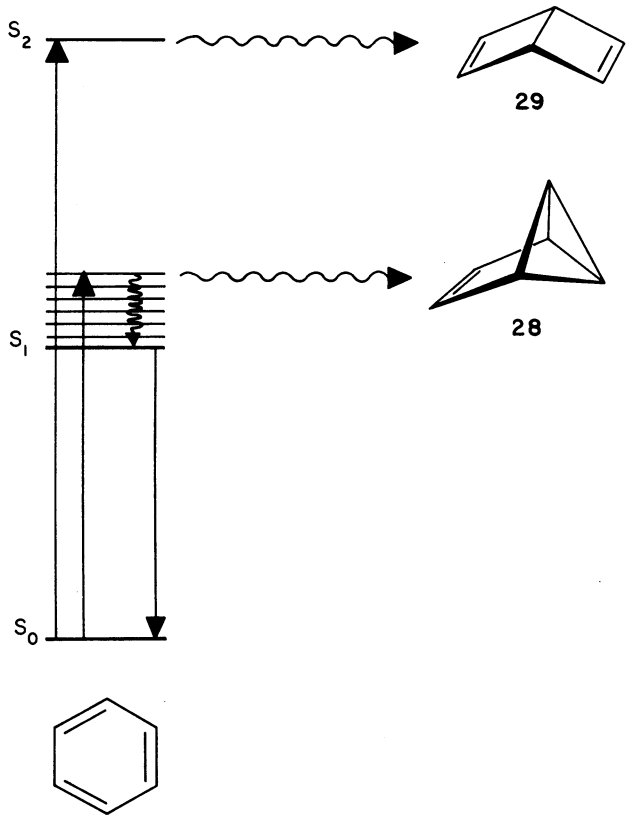


FIGURE 68

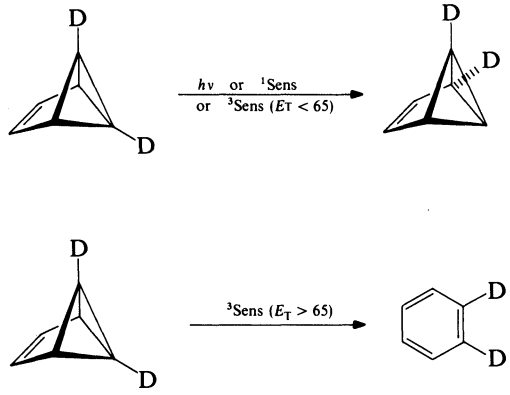


FIGURE 69

B. Photochemistry of Bicyclo[1.1.0]butane

Vacuum ultraviolet (185 nm) photolysis of bicyclo[1.1.0]butane results in the formation of butadiene and cyclobutene in a 10:1 ratio[126]. The butadiene could arise by a path analogous to the thermal cleavage (**a** in Figure 70) or by way of a cyclobutane-1,3-diyl (**b** in Figure 70). The latter mechanism would also provide a route to the cyclobutene. It might appear that the pathways **a** and **b** could be distinguished by deuterium labeling. In fact, when bicyclobutane-2,2,4,4-d_4 was photolyzed it gave a 2:1 mixture of butadienes **30** and **31** (Figure 71). This might seem to imply a 2:1 ratio of mechanisms **b**:**a**, however there is an alternative explanation. It could be that conversion of excited bicyclobutane to butadiene occurs adiabatically and that the excited butadiene undergoes secondary isomerization by way of 3-butenylidene (Figure 72). If this were the explanation, the 2:1

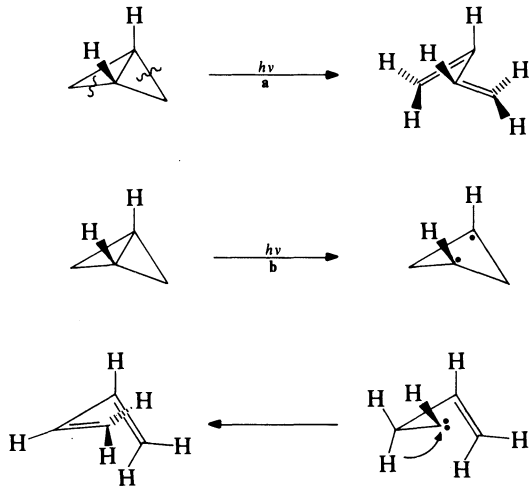


FIGURE 70

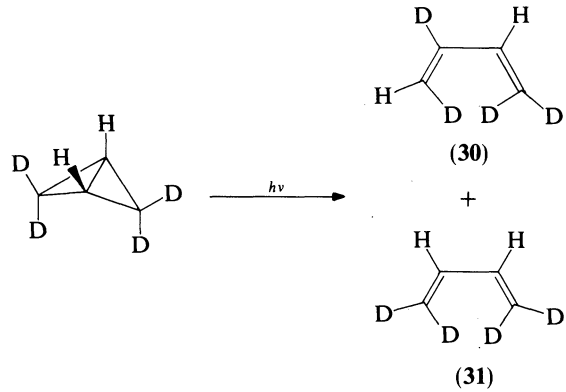


FIGURE 71

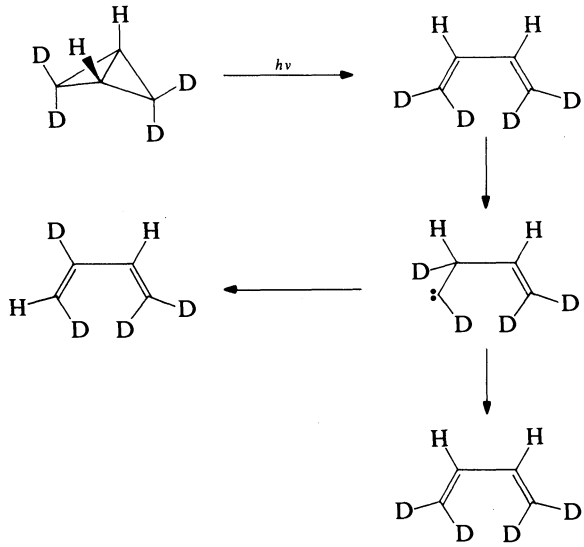


FIGURE 72

product ratio would be interpreted as a primary isotope effect. In order to distinguish among these possibilities bicyclobutane-2-^{13}C was photolyzed. The butadiene product was found to have 2/3 of the label at C(1) and 1/3 at C(2), consistent with the competitive pathways but not with the adiabatic transformation.

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CHAPTER **18**

Cyclopropanes having extra strain

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I. INTRODUCTION

The details of any discussion of strain energy are very dependent on the model chosen and this chapter is no exception. However, this fact should not detract from the fact that extra or reduced strain of substituted species relative to the parent hydrocarbon are real phenomena which may be correlated with the degree of reactivity or ease of isomerization. The present chapter begins with a quantitation of the stabilization and destabilization energies and enthalpies associated with monosubstituted cyclopropanes. The approach involves collection of all relevant thermochemical and good calculational data. Conclusions concerning the sensitivities of cyclopropanes to conjugative and electrostatic effects are drawn from both qualitative theory and formal correlation analysis of these

values. These conclusions are then compared with those of similar treatments of ethylenes as well as other analogues.

Next we focus on fluorinated cyclopropanes where we discuss, for example, the fact that 1,1-difluorocyclopropane and hexafluorocyclopropane show unusual behavior which in part or whole reflects extra strain. Contrariwise, cyclopropanes and other strained molecules substituted by perfluoroalkyl groups such as CF_3 are anomalously stable despite having some slight extra strain.

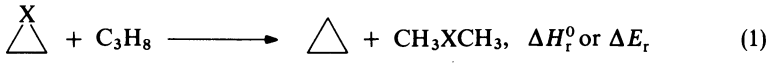
We then turn to radical cations of cyclopropanes as they usually have an energy relationship among the isomers considerably different from that among the neutrals. Implicitly, this also means that the strain energies will be different for the radical cations. Furthermore, in removing a bonding electron certain non-conventional isomeric structures, having no stable neutral analogues become comparable in stability to 'normal' radical cations formed by merely removing an electron. Radical cations and their associated energetics will be explored for cyclopropanes and cyclopropenes in which substitution has been taken so broadly as to include benzvalene, bicyclobutane, cyclopropenone, cyclopropanone, hexafluorocyclopropane and 3,3′-bicyclopropenyl.

Even without prodding by loss of an electron, extreme strain in a cyclopropane, when accompanied by stabilization in a valence tautomer, may combine to gently 'vanish' the three-membered ring. Thus, either geometrical constraints or substituents may cause a cyclopropane not to be a cyclopropane. This topic furnishes the concluding section of our chapter.

It must be emphasized at the outset that we have not attempted to write an exhaustive review but rather a chapter which provides, in modest detail, a discussion of subtopics associated with cyclopropanes having extra or reduced strain. Making use of literature citations through June 1985, this choice of coverage reflects, understandably we hope, our areas of greatest interest in this field.

II. QUALITATIVE MEASURES OF INCREASED STRAIN

Substituted cyclopropanes may be said to have extra strain if the homodesmotic equation (1) is exothermic[1,2]. Similarly, reduced strain is said to be present

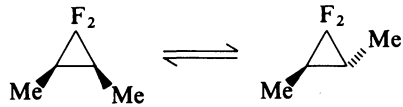


$$+ C_3H_8 \longrightarrow + CH_3XCH_3, \quad \Delta H_r^0 \text{ or } \Delta E_r \qquad (1)$$

(X = CHF, CHMe, CF_2, C=O, $C=CH_2$, etc)

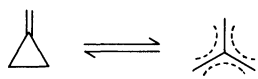
if the reaction is endothermic. It is fairly obvious that this is an operational thermodynamic definition in the sense that what one really observes is an overall destabilization or stabilization of the cyclopropane compared to an acyclic model. For example, an apparent overall stabilization might largely be due to an increased bond order between a ring carbon and a substituent due to resonance. A detailed study of the electron contours and charge densities might actually show that the difference between the center of maximum orbital overlap and the internuclear axis is greater than in the parent cyclopropane. Thus, according to our bonding concept of the origin of strain in cyclopropane, we might consider the ring to be more strained but the substituted molecule to be more stabilized. Presently, not much work has been done in the area of investigation of the effects of substituents on ring electronic distributions in such molecules[3]. Therefore, we will stay with our operational thermochemical definition, always mindful of its implicit ambiguities. We have previously discussed the effects of substituents on the energetics and structures of strained molecules[2,4,5].

What is the significance of added or reduced strain in substituted cyclopropanes? In certain instances the effects of increased strain are immediately evident in reduced energies of activation for selected chemical reactions. This is well illustrated by the ca. 10 kcal mol^{-1} reduction in the geometric isomerization barrier in *cis*-1,1-difluoro-2,3-dimethylcyclopropane (**1**) relative to that in *cis*-1,2-dimethylcyclopropane[6] which appears to be largely due to increased ring strain[7] (cf. equation 2). The ring strain in hexafluorocyclopropane, based on $\Delta H_f^\circ = 233.8$ kcal mol^{-1} [8] and a $-CF_2-$ group increment[9], is calculated to be 54 kcal mol^{-1}. This probably accounts in part for the relative ease of thermal extrusion of CF_2 from this molecule[10] although singlet CF_2 is itself extremely stable. It should also be noted that hexamethoxycyclopropane readily extrudes the carbene but the kinetics are much more complex[11].



(1) (2)

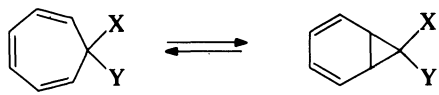
The strain energy of methylenecyclopropane (**2**) exceeds[4] that of cyclopropane by about 13 kcal mol^{-1}, a value similar to the excess strain in 1,1-difluorocyclopropane. This is certainly a part of the propensity for ring-opening although the stability of trimethylenemethane (**3**) is undoubtedly the more important factor (cf. equation 3). Similarly, the ring-opening facility of cyclopropanone (see Chapter 23 by Wasserman and coworkers) partially reflects additional ring strain.



(2) (3) (3)

It is, however, important to point out that strain and reactivity do not necessarily always follow parallel trends. For example, strained ring compounds substituted by trifluoromethyl and general perfluoroalkyl groups are greatly stabilized thermally. This phenomenon has been termed[12] the 'perfluoroalkyl (R_f) effect'. However it appears to be purely kinetic in origin since CF_3 groups appear to increase strain very slightly[13].

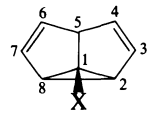
It has been known for many years that substituents can change the position of the tropylidene–norcaradiene (**4** ⇌ **5**) equilibrium (equation 4). While the parent compound



(4) (5) (4)

(X = Y = H) is found exclusively as tropylidene (cycloheptatriene), π-withdrawing substituents (X = Y = CN[14]; X = COOH, Y = H[15]) stabilize the norcaradiene structure. These observations are rationalized purely on structural grounds: π-withdrawing substituents are expected to shorten the distal (2–3) bond and lengthen the vicinal (1–2, 1–3) bonds thus favoring the cyclic structure[16]. This view has sometimes been loosely interpreted as implying thermodynamic stabilization of the cyclopropane by such substituents. However, it was recently calculated that most of the effect on the equilibrium

of equation (4) where cyano substituents are attached is due to destabilization of tropylidene isomer; thermodynamic stabilization of the substituted norcaradiene appears to be very small[17]. The situation for π-donor substituents is more complex. Although, the original prediction[16] was for an increase in all cyclopropane bond lengths induced by π-donors, subsequent studies have established that this is not the case for neutral substituents[18]. Only where the substituents are exceedingly strong π-donors (e.g. O^-, CH_2^-) does this prediction appear to be borne out[19]. Lengthening of the three cyclopropane ring bonds in cyclopropoxide and cyclopropylcarbinyl anion would appear to increase ring strain but the overall effect is stabilization[5]. Aminocyclopropane has very slight thermodynamic stabilization (if any) if one employs equation 1 (i.e. 'isopropyl stabilization' energy or enthalpy) as a criterion[5,20]. This is consistent with its structure[21], and photoelectron spectrum[22] which imply little conjugation of the substituent with the ring. The photoelectron spectrum of cyclopropylamine and other substituted cyclopropanes are discussed by Ballard in Chapter 5 and aminocyclopropanes are described in Chapter 22 by Vilsmaier. These findings appear to be consistent with the position of equilibrium for 7-piperidinotropylidene/norcaradiene[23]. Similar considerations have been applied toward understanding the position of substitution in cyano-[24] and methoxy-[25] semibullvalenes (**6**).



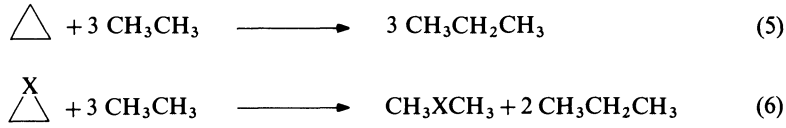
(6)

The substituent-induced changes in the shapes of cyclopropane rings are manifested in the regiospecificity of hydrogenation reactions which preferably break the longest bond[26]. They have also been employed in general organic synthesis[27].

III. QUANTITATION OF SUBSTITUENT EFFECTS ON STRAIN

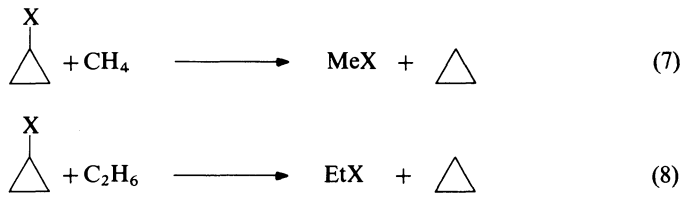
There are very few published thermochemical data for substituted strained cyclopropanes[28,29] of any cycloalkanes). Furthermore, enthalpy of combustion data must only be accepted after proper caution especially for studies of small magnitude effects such as we are describing. For example, heats of combustion of substituted cyclopropanes may be in the order of 1000 kcal mol^{-1}. Accuracy of only 99.5% would yield an uncertainty of ± 5 kcal mol^{-1} which is greater than many of the substituent effects reported in this work[30]. The thermochemistry of cyclopropanes is discussed in Chapter 1 by Wiberg. The approach that we have employed to make up for the lack of thermochemical data is to employ split basis set *ab initio* molecular orbital calculations on optimized or virtually optimized substituted molecules. While our initial work with the STO-3G basis set provided good qualitative insights[2], it quickly became apparent that higher order basis sets were required both to calculate reasonable molecular structures and to achieve good stabilization energies. For example, the experimental enthalpy of hydrogenation of 1,1-difluoroethane disagreed with the (appropriately scaled) STO-3G value by 19 kcal mol^{-1}, while the discrepancy was only 1 kcal mol^{-1} for the 4-31G basis set[7]. The 4-31G basis set was therefore employed for the bulk of our investigation.

Equation 1 is a 'homodesmotic' reaction[1], having the same numbers and types of structural units on both sides of the equation. Note that the cyclopropyl position (2° carbon) is modelled by the isopropyl carbon (also 2°). It is worth noting briefly that



equation 1 is the difference of two group separation reactions (5 and 6). Equation 5 gives the strain energy of cyclopropane itself. Equation 6 gives the strain energy of the substituted cyclopropane (or heterocyclopropane). Both strain energies are defined relative to the corresponding isopropyl-type species. This is a particularly useful definition, aside from the fact that the substituted carbons are of the same type, since actual chemical reduction of the distal bond provides the isopropyl analogue. Furthermore, other reactions such as the geometric isomerization of 1,1-difluoro-2,3-dimethylcyclopropane provide diradicaloids reminiscent of isopropyl models.

Unfortunately, good calculational as well as thermochemical data are not often published for isopropyl derivatives. They are more commonly available for methyl and ethyl derivatives. Thus, equations 7 and 8 define 'methyl' and 'ethyl' stabilization energies respectively for cyclopropanes



These equations are termed 'isodesmic' rather than 'homodesmotic'. While they are less perfect models than the homodesmotic isopropyl comparison, they have the advantage of more available data. In general, both isodesmic and homodesmotic comparisons tend to cancel out errors due to basis set deficiencies, lack of configuration interaction and neglect of electron correlation. These features allow one to obtain meaningful stabilization and destabilization energies from comparatively enormous total energies. In our present discussion it is obvious but worth reminding the reader that both calculated total energies and experimental $\Delta H_f(g)$ refer to isolated gas phase molecules. Furthermore, the molecules examined are hypothetical vibrationless structures having equilibrium value bond lengths. Standard conditions (298 K, 1 atm) obviously refer to molecules having a characteristic distribution of vibrational states including the zero point energy.

In Table 1 we list calculated (4-31G) and experimental stabilization energies for a variety of monosubstituted cyclopropanes[5]. Some interesting trends occur. First, there is a good correspondence between experimental and calcualted stabilization energies. One notable exception is the 6.1 kcal mol^{-1} discrepancy for vinylcyclopropane and here we feel that the experiment should be redone. The Pierson linear regression coefficient (r) between experimental stabilization enthalpies and calculated stabilization energies is 0.96 ($n = 6$, standard error = 0.81 kcal mol^{-1}) for the methyl comparison, 0.99 ($n = 6$, standard error = 0.34 kcal mol^{-1}) for the ethyl comparison and 0.91 ($n = 4$, standard error = 0.98 kcal mol^{-1}) for the isopropyl comparison[5].

It is also apparent that the degree of stabilization generally follows the order: isopropyl < ethyl < methyl, except for electropositive substituents such as Li and BH_2 where the order is reversed. These trends, noted by others[20], will be explained in due course. It is worth noting that calculated and experimental isopropyl stabilizations

TABLE 1. Calculated and experimental stabilization energies of substituted cyclopropanes, cyclopropyl-X (in kcal mol^{-1})*

Stabilization energy model	Methyl		Ethyl		Isopropyl			
X	ΔE^a_{stab}	ΔH^b_{stab}	ΔE^a_{stab}	ΔH^b_{stab}	ΔE^a_{stab}	ΔH^b_{stab}	ΔE^c_{stab}	ΔE^d_{stab}
H	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Cl								
F	5.3		−1.1		−6.2		−5.1	−5.3
Me	2.7	4.2	1.6	1.6	1.0	−0.6	0.4	1.1
OMe	5.3		0.5					
OH	5.9		1.9		−2.7		−2.6	−2.0
NH_2	6.5	6.6	4.4	3.0	1.2	−0.7	1.0	4.0
OAc								
CH_2^-								
O^-	12.0		8.7		2.3			
NH_3^+	6.3	7.5	1.0	1.0	−3.0	−5.1		
CN	2.8	4.5	1.8	1.3		−0.1	1.1	1.0
NC	3.4		0.5				−2.1	−1.9
CHO								
COMe	6.6	7.0	5.0	3.6		3.4		
COOMe		6.1		3.9		2.2		
NO_2	4.5		0.8					
CF_3								
Li	−2.1		2.9		6.2			
BH_2	6.1		9.4		8.9			
CH_2^+	33.7		27.1					
CH_2=CH–	2.7	0.6[e]	2.9	−3.2[e]				
HC≡C–	1.7		1.0					

[a] 4-31G calculated energies used.
[b] Experimental heats of formation used.
[c] 3-21G//3-21G results[31,32].
[d] 6-31G*//3-21G results[32].
[e] This value was not included in the statistical correlations because we do not believe that conjugation of vinyl and cyclopropyl is destabilizing.
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indicate destabilization by F, NH_3^+ and probably OH. Isopropyl stabilization by F and OH as well as NC have been predicted at both the 3-21G[31] and 6-31G[32] levels. It is clear that NH_3^+ is an electronegative substituent having negligible resonance interactions. By analogy to substituted olefins[33], where it is known that electronegative substituents are thermodynamically destabilizing[34], one expects destabilization of cyclopropane by NH_3^+. Similarly, if the electronegative F and OH substituents have little tendency to conjugate with the ring[20], one anticipates destabilization. Although the isocyano group could be a π-withdrawer its σ_R value (−0.01) indicates[35] that it is weakly so and its σ_I value indicates electronegativity perhaps representable by the resonance contribution–$N^+\equiv C:^-$. Thus, this substituent is reminiscent of NH_3^+ and logically destabilizing. The effects of Me, NH_2, and CN in this series are weak and ambiguous. Certainly the NH_2 effect is consistent with the earlier-cited structural and photoelectron spectroscopic results. The result for cyano is consistent with the earlier discussed conclusions of Ref. 17. Large isopropyl stabilizations are predicted here for cyclopropane rings substituted by the very strong π-acceptors BH_2 and CH_2^+. Cyclopropylcarbinyl cations and related structures and their chemistry are

discussed in much greater depth in Chapter 11 by Friedrich. In contrast to cyclopropylcarbinyl cation, the isopropyl stabilization in cyclopropoxide is calculated to be fairly small.

Table 2 lists calculated and experimental stabilization energies and enthalpies for substituted ethylenes. Similar trends are seen when compared to the cyclopropyl series: methyl stabilization exceeds ethyl which exceeds isopropyl stabilization energies except for the electropositive substituents where the reverse order is obtained. 'Stabilization' or 'destabilization' may in fact depend strongly upon the model employed. For example, the 4-31G results for vinyl fluoride suggest stabilization if methyl fluoride is the model and destabilization if isopropyl fluoride is the model. This is analogous to the comparison between methyl, vinyl, and isopropyl cations wherein the first of these is so small that it cannot efficiently delocalize its charge as well as larger species. Again strongly electronegative substituents (Cl, OAc, NH_3^+, NO_2) are destabilizing when the isopropyl model is considered. An interesting counterpoint to the cyclopropyl species is that in the vinyl series greater stabilization is found when the substituent is O^- than for CH_2^+ in marked contrast to the cyclopropyl cases.

TABLE 2. Calculated and experimental stabilization energies of substituted ethylenes, vinyl-X (in kcal mol^{-1})*

Stabilization energy model	Methyl		Ethyl		Isopropyl	
X	ΔE^a_{stab}	ΔH^b_{stab}	ΔE^a_{stab}	ΔH^b_{stab}	ΔE^a_{stab}	ΔH^c_{stab}
H	0.0	0.0	0.0	0.0	0.0	0.0
Cl	12.8	5.7		0.8		−2.2
F	6.4	6.7	0.0	3.3	−5.1	0.6
Me	4.3	5.4	3.2	2.8	2.6	0.6
OMe	10.9	12.3	6.1	6.9		3.3
OH	10.6	11.9	6.6	6.3	1.9	2.2
NH_2	13.3	13.3	11.2	9.7	8.0	6.2
OAc		7.6		1.8		−2.3
CH_2^-	39.6		35.0			
O^-	38.6	30.1	35.3	22.4	28.9	17.0
NH_3^+	1.5	4.9	−3.9	−1.6	−7.8	−7.7
CN	3.3	4.8	2.4	1.7		0.2
NC	5.8		2.8			
CHO	6.4	6.9[c]	4.5	4.0[c]		2.2[c]
COMe	3.9	10.5	2.4	7.2		6.9
COOMe	8.0	11.9	2.0	9.5		8.0
NO_2	4.7	3.4	1.1	−0.8		−4.7[d]
CF_3	−0.2	−1.7	−2.5			
Li	4.8		9.2		8.7	
BH_2	5.9		9.2		8.7	
CH_2^+	30.0	23.3	23.3	14.6		10.5
CH_2=CH–	7.8	8.8	8.0	6.2		4.7
HC≡C–	3.9	5.9	3.3	3.1		1.1

[a] 4-31G calculated energies used.

[b] Experimental heats of formation used. All $\Delta H_f^\circ(g)$ values from Ref. 28.

[c] If the $\Delta H_f^\circ(g)$ estimated by Hegedus and Harrison (V. I. Hegedus and A. G. Harrison, *Int. J. Mass Spectrom. Ion Phys.*, **30**, 293 (1979)) is used, the stabilization energy would be overestimated as compared to the value listed.

[d] The $\Delta H_f^\circ(g)$ for CH_2=$CHNO_2$ estimated in Ref. 5 was used rather than that earlier estimated by Shaw (R. Shaw, *Int. J. Chem. Kinet.*, **5**, 261 (1973)).

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In order to gain further insights from the above thermochemical substituent effects we have employed the techniques of linear free energy relationships and specifically applied correlation analysis using the Dual Substituent Parameter (DSP) approach of Taft's group[36]. The actual substituent constants are from a recent compilation[35]. Before discussing our results we must present three brief caveats. The substituent σ_I and σ_R, employed by Taft as well as the earlier Hammett constants and most of the variations thereof are based upon systems X–G–Y where Y is the reaction site attached to hydrocarbon framework G to which substituent X is attached. The present treatment considers X–G, a case for which the substituents were not originally designed. Second, for our purposes we must treat π-acceptors and π-donors separately since they are both stabilizing (in the absence of inductive effects) yet their σ_R of course have opposite signs. Finally, because the data sets must be split into π-donors and π-acceptors, we are reduced to 5–8 data points for each DSP correlation. Correlations involving two independent variables and only 5–8 data points cannot be interpreted too quantitatively. Therefore, we consider our DSP correlations to be semiquantitative. The DSP equation is equation (9)

$$E_{stab} = m_I\sigma_I + m_R\sigma_R + b \tag{9}$$

where m_I, m_R and b are constants.

TABLE 3. Energies by equation 9 (in kcal mol^{-1})*

	n	m_I	m_R	b	$R^{2,g}$	R^h	Std error
			(a) Methyl stabilization				
Vinyl-X							
(π-donors)[a]	6	−4.36	−17.62	0.73	0.97	0.99	1.07
(π-acceptors)[b]	8	4.30	14.35	0.83	0.22	0.47	3.05
(π-acceptors)[c]	5	3.25	21.38	0.02	0.83	0.91	1.37
Cyclopropyl-X							
(π-donors)[a]	6	1.78	−7.36	0.71	0.95	0.98	0.69
(π-acceptors)[d]	5	2.90	25.98	0.12	0.91	0.95	1.05
			(b) Ethyl stabilization				
Vinyl-X							
(π-donors)[a]	6	−15.27	−17.10	0.15	0.99	0.996	0.47
(π-acceptors)[b]	8	1.27	10.57	0.01	0.15	0.38	2.30
Cyclopropyl-X							
(π-donors)[a]	6	−9.32	−6.87	0.12	0.94	0.97	0.63
(π-acceptors)[d]	5	−1.32	24.24	0.25	0.90	0.95	0.90
			(c) Isopropyl stabilization[e]				
Vinyl-X							
(π-donors)[f]	5	−22.32	−13.80	−0.01	0.97	0.99	1.09
Cyclopropyl-X							
(π-donors)[f]	5	−15.88	−4.00	−0.00	0.93	0.97	1.16

[a] Substituents: H, F, Me, OMe, OH, NH_2.
[b] Substituents: H, CN, NC, CHO, COMe, CO_2Me, NO_2, CF_3.
[c] Substituents: H, CN, CHO, COMe, NO_2.
[d] Substituents: H, CN, NC, COMe, NO_2.
[e] There were only enough data to correlate π-donors.
[f] Substituents: H, F, Me, OH, NH_2.
[g] R^2 is the correlation of determinacy.
[h] R is the correlation coefficient.

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The DSP correlations are presented in Table 3. Generally, these correlations are better for π-donors than for π-acceptors. We will comment briefly on a few points. First, as we go from methyl to ethyl to isopropyl stabilization, m_I becomes more negative having the effect of decreasing stabilization energies for electronegative substituents when σ_I is positive. For electropositive substituents (i.e. with negative σ_I) one would naturally expect to see increased stabilization. This is the trend observed here[5] and previously discussed[20]. The values for m_R are much more constant and are not so model-dependent. A second striking point is that for the cyclopropyl series, m_R (acceptors) is much larger in magnitude than m_R (donors). Thus, cyclopropyl appears to be a strong π-donor and a very weak π-acceptor. The latter observation is consistent with the very low barrier (1.1 kcal mol^{-1}) to methylene rotation in the cyclopropylcarbinyl anion[19] and the very small conjugative stabilization in this species[37]. It is also consistent with the dominance of inductive effects on the stabilization energies of cyclopropanes substituted by π-donors noted by others[20], since for isopropyl stabilization of cyclopropyl molecules substituted by π-donors, m_I is about four times the magnitude of m_R. Another interesting point is that, using methyl and ethyl stabilization energies as criteria, cyclopropyl appears to be a stronger π-donor than vinyl. This contrasts with the conclusion based upon analysis of X-ray data[18] wherein cyclopropyl was said to be only about 70% as effective a π-donor as vinyl. However, others have indicated that cyclopropane may indeed be a stronger π-donor than vinyl[38]. Significant rotational barriers are found in 2,2-dimethylcyclopropylcarbinyl cation[39], nitrocyclopropane[40], 1,1-bis(1-nitrocyclopropyl)[41], cyclopropanecarboxaldehyde[42], cyclopropyldifluoroborane[43], cyclopropylcarbonyl fluoride[44], cyclopropyldichloroborane[45] and cyclopropylcarbonyl chloride[46].

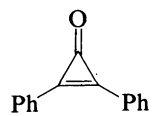
Another approach employing linear free energy relationships and correlation analysis depends upon a theoretical set of substituent parameters developed by Topsom and coworkers[47]. The correlation involves three substituent parameters: σ_{R°, a resonance parameter; σ_F, a field effect parameter which is virtually identical[5] to σ_I; and σ_X, an electronegativity parameter. The correlations (equation 10) are displayed in Table 4.

$$E_{stab} = m_X\sigma_X + m_F\sigma_F + m_{R^\circ}\sigma_{R^\circ} + b \tag{10}$$

These correlations, more relevant for the G–X case, provide essentially similar conclusions to those of the Taft DSP approach.

The relatively strong π-donor ability of cyclopropane is consistent with its comparatively low adiabatic ionization potential, the energy difference between a molecule and its derived cation when both are in their most stable geometries. In Table 5 are listed m_R values obtained using the DSP approach (Table 3) for the vinyl and cyclopropyl series as well as those for the ethynyl and phenyl cases. For the parent hydrocarbons, there is a nice correlation between m_R for the π-acceptors and IP_{adiab}. Why is cyclopropane such a poor π-acceptor compared to vinyl (i.e. why is the m_R value for π-donor substituents so low)? It is clear that of the four hydrocarbons shown, cyclopropane has the least affinity for electrons. (For none of the hydrocarbons is the added electron in fact bound. The electron affinities given are thus vertical quantities, i.e. those for which the geometry of the anion is the same as the original neutral molecule.)

It is worthwhile to dwell briefly upon the topic of substituent effects on cyclopropenes. The most striking substituent effect may be seen in cyclopropenes such as diphenylcyclopropenone (7). This interaction between ring and ketone substituent is so strong as to



(7)

(8)

TABLE 4. Energies[a] by equation 10 (in kcal mol^{-1})*

	n	m_X	m_F	m_R^0	b	R	R^2	Std error
				(a) Methyl stabilization				
Vinyl-X								
(π-donors)	6	15.98	−14.55	−18.73	−0.10	0.99	0.997	0.59
(π-acceptors)	8	37.15	−20.89	17.05	1.24	0.57	0.82	2.22
Cyclopropyl-X								
(π-donors)	6	11.24	−5.31	−5.83	0.09	0.98	0.99	0.54
(π-acceptors)	5	41.45	−26.23	29.10	−0.09	0.99	0.99	0.56
HC≡C-X								
(π-donors)	6	33.89	−77.77	−20.80	0.09	0.996	0.998	0.87
(π-acceptors)	8	96.93	−80.51	−14.92	5.50	0.70	0.84	5.42
Phenyl-X								
(π-donors)	6	−3.68	9.09	−15.18	0.14	0.95	0.98	1.32
(π-acceptors)[b]	4	27.39	−22.55	35.70	—	—	—	—[d]
				(b) Ethyl stabilization				
Vinyl-X								
(π-donors)	6	7.03	−20.19	−21.53	−0.05	0.99	0.99	0.70
(π-acceptors)	8	32.47	−20.82	12.38	0.34	0.80	0.89	1.25
Cyclopropyl-X								
(π-donors)	6	2.07	−11.18	−8.95	0.15	0.92	0.96	0.90
(π-acceptors)	5	42.23	−31.15	24.78	0.12	0.97	0.98	0.73
HC≡C-X								
(π-donors)	6	25.55	−84.01	−23.35	0.14	0.99	0.997	1.23
(π-acceptors)	8	94.69	−82.83	−28.54	5.00	0.71	0.85	5.77
Phenyl-X								
(π-donors)	6	−12.66	3.44	−17.95	0.33	0.87	0.93	1.62
(π-acceptors)[b]	4	63.23	−48.04	28.99	—	—	—	—[d]
				(c) Isopropyl stabilization[c]				
Vinyl-X	5	4.15	−6.71	−19.00	−0.03	1.00	1.00	0.45
Cyclopropyl-X	5	1.16	−18.64	−6.32	0.02	1.00	1.00	0.26
HC≡C-X	5	25.15	−91.78	−20.70	0.02	1.00	1.00	0.31
Phenyl-X	5	−11.96	−5.22	−15.38	0.07	0.97	0.98	1.06

[a] The same substituents were employed for each correlation as in Table 3.
[b] This is not statistically valid because a perfect line fit is forced with using only four points.
[c] There were only enough data for correlations with π-donors.
[d] The F-level or tolerance level is not sufficient for the program to determine the constant term.
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provide 22 kcal mol^{-1} of resonance stabilization to the three-membered ring thus giving it about two-thirds of the total aromatic stabilization of benzene[48]. It is worthwhile noting that the recently characterized methylenecyclopropene (**8**) also appears to be aromatic[49]. An unusual aspect of cyclopropene is the striking ability of σ-bonded substituents at C(3) to conjugate with the double bond. Homodesmotic equations 11–13, based upon 4-31G

TABLE 5. Relationships of conjugation sensitivity slopes (m_R) to ionization potentials and electron affinities of parent hydrocarbons*

		(a) π-acceptors Hydrocarbon	
Parent hydrocarbon	m_R	IP_{adiab} (eV)	IP_{vert} (eV)
Vinyl-X	14.4	10.51[a]	10.51[b]
Cyclopropyl-X	26.0	9.86[c]	10.60, 11.30[d]
HC≡C-X	7.8	11.40[a]	11.40[b]
Phenyl-X	28.1	9.25[a]	9.25[b]

		(b) π-donors Hydrocarbon
Parent hydrocarbon	m_R	EA^{e}_{vert} (eV)
Vinyl-X	−17.6	−1.78
Cyclopropyl-X	−7.4	−5.29[f]
HC≡C-X	−20.9	−2.6
Phenyl-X	−10.9	−1.15

[a] See Ref. 22.
[b] This value was approximated from those in R. D. Levin and S. G. Lias, *Ionization Potential and Appearance Potential Measurements, 1971–1981*, National Bureau of Standards, US Department of Commerce, NSRDS-NBS 71 (1982).
[c] S. G. Lias and T. J. Buckley, *Int. J. Mass Spectrom. Ion Proc.*, **56**, 123 (1984).
[d] H. Basch, M. N. Robin, N. A. Kuebler, C. Baker and D. W. Turner, *J. Chem. Phys.*, **51**, 52 (1969).
[e] These values were obtained from K. D. Jordan and P. D. Burrow, *Accts Chem. Res.*, **11**, 341 (1978) and K. D. Jordan, personal communication.
[f] A. E. Howard and S. W. Staley, in *ACS Symposium Series, No. 263, Resonances in Electron-Molecule Scattering, Van der Waals Complexes and Reactive Dynamics*, (Ed. D. G. Truhlar), American Chemical Society, Washington, D. C., 1984, p. 183.
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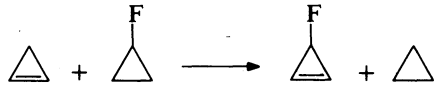
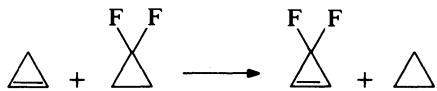
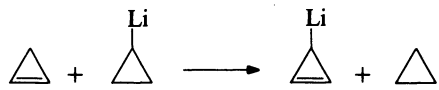
calculational data, indicate stabilization in 3-fluorocyclopropene and 3,3-difluorocyclopropene that perhaps hints of aromaticity, while destabilization in 3-lithiocyclopropene hints of antiaromaticity. 1-Fluorocyclopropene is highly destabilized as is fluoroacetylene while 1-lithiocyclopropene is highly stabilized as is lithioacetylene. 3-Fluorocyclopropene



$$\Delta E_{4\text{-}31G} = -8.1 \text{ kcal mol}^{-1} \quad (11)$$

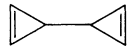


$$\Delta E_{4\text{-}31G} = -9.6 \text{ kcal mol}^{-1} \quad (12)$$



$$\Delta E_{4\text{-}31G} = +3.6 \text{ kcal mol}^{-1} \quad (13)$$

can be studied at $-50°C$ and its J_{HF}^{gem} appears to indicate an unusually large FCH angle[50] which could well enhance the molecule's aromaticity. 3,3'-Bicyclopropenyl (**9**) maintains a



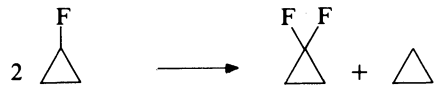
(**9**)

strong interaction between its double bonds through interaction between C(3) and C(3')[51,52]. Discussions of cyclopropenes and aromatic cyclopropenyl derivatives are presented in Chapter 21 by Halton and Banwell, and in Chapter 24 by Billups and Moorehead.

IV. HIGHLY FLUORINATED STRAINED MOLECULES

It was previously noted that fluoro substitution significantly increases strain in cyclopropane rings. An increment of 4.5–5 kcal mol^{-1} of extra strain per fluorine attached to cyclopropane had earlier been indicated[53]. The calculated extra strain energies in fluorocyclopropane (Table 1), 1,1-difluorocyclopropane[7] (11.7 kcal mol^{-1}) and hexafluorocyclopropane (27 kcal mol^{-1}; see earlier discussion) are very close to this prediction. This is actually somewhat startling since gem-difluoro groups have large added stabilizations (IGSTAB = Incremental Geminal Stabilization[7], which are significantly decreased in cyclopropanes and even further in olefins (equations 14–16).

$$2\ MeCH_2F \longrightarrow MeCHF_2 + MeMe \qquad \begin{aligned}\Delta E_{4\text{-}31G} &= -9.2\ \text{kcal mol}^{-1}\\ \text{IGSTAB} &= -4.6\ \text{kcal mol}^{-1}\end{aligned} \qquad (14)$$



$$2\ \Delta E_{4\text{-}31G} = -5.2\ \text{kcal mol}^{-1}$$
$$\text{IGSTAB} = -2.6\ \text{kcal mol}^{-1} \qquad (15)$$

$$2\ CH_2{=}CHF \longrightarrow CH_2{=}CF_2 + CH_2{=}CH_2 \qquad \begin{aligned}\Delta E_{4\text{-}31G} &= -1.6\ \text{kcal mol}^{-1}\\ \text{IGSTAB} &= -0.8\ \text{kcal mol}^{-1}\end{aligned} \qquad (16)$$

It is worthwhile to re-emphasize briefly how model-dependent strain is at this point. If we employ the value for the ethyl stabilization (ΔH_{stab}) for fluoroethylene (Table 2) we conclude that this molecule is stabilized. This is not a specious comparison since this model is relevant to an actual chemical reaction (hydrogenation literally and addition reactions generally). Since equation 16 is exothermic, it appears that 1,1-difluoroethylene is even slightly stabilized relative to fluoroethylene. Yet it is widely known that such gem-difluoroalkenes are highly reactive and presumably very destabilized. The apparent dichotomy is resolved when one realizes that referencing 1,1-difluoroethylene to two fluoroethylene molecules is not as reasonable a comparison as referencing it to 1,1-difluoroethane (i.e. the reduction reaction again). The exothermicity of reaction 17, which is identical to the difference between enthalpies of hydrogenation of ethylene and 1,1-difluoroethylene indicates ca. 7 kcal mol^{-1} of destabilization in the latter consistent with its instability.

$$CH_3CH_3 + CH_2 = CF_2 \rightarrow CH_3CHF_2 + CH_2 = CH_2 \quad \Delta H = -7.2\ \text{kcal mol}^{-1} \qquad (17)$$

Here is another instance of the extreme model dependency of strain energies in the fluorocarbon series. A strainless $C(F)_2(C)_2$ group increment of -104.9 kcal mol^{-1} had earlier been derived[54]. In principle, one might expect that this increment would be applicable to calculating the strain energy of hexafluorocyclopropane. Applying this value, we concluded[7] that the total strain in the molecule was 80.9 kcal mol^{-1}. This was even higher than the value calculated by Bernett some years earlier[55], 68.6 kcal mol^{-1}. We were buoyed by the fact that the endothermicity of equation 18 indicated a strain of

$$3\,C_3F_8 \longrightarrow \text{  } + 3\,C_2F_6 \quad \Delta H = 76.7\ \text{kcal mol}^{-1} \tag{18}$$

76.7 kcal mol^{-1} using a totally different model system[7]. However, what is the proper enthalpy increment for a strainless CF_2 group[56] of the type relevant to the case at hand? A simple analysis indicates that perfluorocyclohexane might be a particularly good model since $-CF_2-$ groups are attached to $-CF_2-$ groups as they are in the cyclopropane and the model system is presumed to be virtually strainless. When cyclohexane is employed as the source of a strainless $C(H)_2(C)_2$ group increment, this 'diagonal approach'[57] yields -4.92 kcal mol^{-1}, a value virtually identical with those obtained by various homodesmotic equations as well as Benson's strainless group increment. The $\Delta H_f^\circ(g)$ value[58] for perfluorocyclohexane, -566.2 ± 2 kcal mol^{-1}, leads to a group increment of -94.4 kcal mol^{-1}. This value is about 10 kcal mol^{-1} more positive than the earlier-cited Dolbier value[54] despite the fact that both are $C(F)_2(C)_2$ increments. We will call the newer group increment $C(F)_2(CF_2)_2$. Before commenting further on this difference it is worthwhile examining whether other assumptions provide the same data. One can calculate suitable group increments from equations 19 and 20 and the values are -97.3 and -95.8 kcal mol^{-1} respectively. Equation 19 eliminates C_2F_6 and is less valid as a model than equation 20. Another argument is based upon an assumed heat of formation of

$$\Delta H_f^\circ[C(F)_2(CF_2)_2] = 1/5[\Delta H_f^\circ(CF_3(CF_2)_5CF_3) - \Delta H_f^\circ(C_2F_6)] \tag{19}$$

$$\Delta H_f^\circ[C(F)_2(CF_2)_2] = 1/4[\Delta H_f^\circ(CF_3(CF_2)_5CF_3) - \Delta H_f^\circ(C_3F_8)] \tag{20}$$

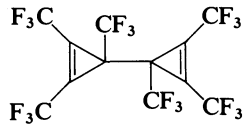
an infinite gaseous chain of $-CF_2-$ (i.e. polytetrafluoroethylene). Combination of the known heat of formation of the solid[28] with an estimated heat of sublimation yields a group increment value of -97.2 kcal mol^{-1} in reasonable agreement with the earlier two cited values. A simple average of the three values yields $\Delta H_f^\circ[C(F)_2(CF_2)_2] = -95.8$ kcal mol^{-1}. It is this value which, when taken with the experimental $\Delta H_f^\circ(g)$ for hexafluorocyclopropane[8] yields a strain energy of 54 kcal mol^{-1}. What is the source of the extra strain? Since F inductively destabilizes the ring, offering no mitigating resonance stabilization, perfluorination greatly destabilizes the ring. However, the simple additivity of strains is the surprising point.

The $C(F)_2(CF_2)_2$ group increment allows evaluation of the strain energy in octafluorocyclobutane. There are three published experimental studies providing $\Delta H_f^\circ(g)$ data for this compound[28, 53, 59]. The first value (taken from Pedley and Rylance's thermochemical archives[28]) is -368.7 kcal mol^{-1} and is based upon reaction with sodium while the O'Neal and Benson value[53] (-367.8 kcal mol^{-1}, if one employs the 'archival' value for C_2F_4) is based upon the experimental equilibrium with tetrafluoroethylene. The third value[59], based upon combustion measurements, is -365.2 kcal mol^{-1} if one employs 'archival' values for the products. The strain energy is thus between 14.5 and 18 kcal mol^{-1}, some 8.5–12 kcal mol^{-1} lower than in the parent hydrocarbon. Why is this value low? One explanation may follow recent work by Wiberg[60]. He concludes that a large part of the strain in cyclobutane is due to repulsion between non-bonded carbons and

shows that electronegative substituents appear to relieve similar strain in the bicyclo [1.1.1] pentane series. Presumably, electron withdrawal decreases non-bonded repulsion in octafluorocyclobutane thus relieving strain.

Why is $\Delta H_f^\circ[C(F)_2(CF_2)_2]$ fully 9 kcal mol^{-1} higher than $\Delta H_f^\circ[C(F)_2(C)_2]$? In other words, why are non-next-nearest-neighbor' corrections so large? One can simply note the high polarity of the C–C bond in $-CH_2-CF_2-$ units and realize that there is a reduced energy increment associated with it.

We conclude this section by briefly noting the immense thermal stabilization conferred upon strained molecules substituted by perfluoroalkyl groups. For example hexakis(trifluoromethyl)-3,3'-bicyclopropenyl (**10**) has a half-life of over 2 hours at



(10)

360°C[61] while strained valence isomers are stabilized[12] relative to hexakis(trifluoromethyl)benzene by over 30 kcal mol^{-1}. Lemal and Dunlap[12] labelled such stability a manifestation of the perfluoroalkyl (R_f) effect' which was said to be both kinetic and thermodynamic in origin and which confers stability on strained carbon frameworks. Subsequent consideration of experimental and calculational data indicated that the CF_3 group is slightly destabilizing thermodynamically on strained and unsaturated carbon frameworks (see Table 2) so that the effect is completely kinetic in nature if one uses acyclic unstrained molecules as models[13]. Here, kinetic stabilization does not at all mirror thermodynamic stabilization, whereas for 1,1-difluorocyclopropane, thermodynamic stabilization is almost quantitatively manifested in kinetic destabilization.

V. THE RADICAL CATIONS OF CYCLOPROPANES WITH ADDITIONAL STRAIN

The radical cations of cyclopropanes are of interest for numerous reasons. The first reason is that because Koopmans' theorem equates (to within a sign) the various ionization potentials of a molecule to its various orbital energies, the ionization process thus gives direct information about the electronic (i.e. orbital) interactions in the molecule (see, for example, Ref. 62). Photoelectron spectroscopy on gas phase species is the method of choice for these investigations. We refer the reader to Chapter 5 by Ballard for a more complete discussion of the method and will quote only a few results.

The ionization process will be discussed in this chapter from the vantage point of strained molecules and their destabilization or strain energies (complementary vantage points are discussed by Schwarz in Chapter 4). It is imperative to remember that although the exact values of strain energy are intrinsically very model-dependent, they generally correlate with the relative ordering of the species' thermodynamic stability. Unfortunately, even when the strain energy of the neutral from which the radical cation is derived is well understood, it is not *a priori* obvious whether ionization will increase or decrease the strain energy of a given cyclopropane derivative. To the extent that cyclopropanes are viewed as olefinic so that a derivative would be considered conjugated, loss of an electron is expected to be accompanied by an increase in stability. More properly, because delocalization in ions and radicals is generally greater than in the formally related neutral, closed shell species, the ionized cyclopropane gains stability relative to the corresponding neutral.

Equivalently, the ionization potential is expected to be comparatively low. Contrariwise, to the extent that cyclopropane and its derivatives are strained because of inadequate electron 'glue' (e.g. because of bent bonds and resultant poor C–C overlap), removal of an electron will further destabilize the species—ionization will add to the total strain energy. More properly, the ionization potential is expected to be comparatively high and so the ion loses stability relative to the corresponding neutral. The energetics of the ionization process of cyclopropanes thus provide a fruitful area in the understanding of the energetics of these strained species.

The second reason for interest in radical cations is that they are generally more reactive than the closed shell species from which they are derived. It is thus not surprising that cyclopropanes undergo diverse electrochemical and other electron transfer reactions, topics discussed, and thus largely referred to, by Boche and Becker in Chapters 12 and 15 of this volume. As radiation generally produces radical ions, the reader is referred to Alfassi's contribution, Chapter 14, on radiation chemistry. At least in a formal way, the low-lying excited electronic states of numerous species may be understood as intramolecular complexes of the radical cation and radical anion. However, radical cations may be formed in yet other ways. Among the most efficient 'chemical' alternatives is chemiionization by (electron transfer to) either other radical cations or suitably electron-'hungry' neutrals most notably electronically excited quinones such as chloranil and cyanoarenes such as *p*-dicyanobenzene[63]. The results of these varying methods will be included in this chapter.

The greater reactivity of radical cations, in principle, facilitates interconversion of isomers. With no loss in generality, let A be more stable than its isomer B. With regard to the relative stability of their radical cations, conceptually there are three cases: A^+ is more stable than B^+, A^+ is less stable than B^+, and A^+ and B^+ have precisely equal stability because they are in fact the same ion. All three of these cases have been documented. The first case is expected to facilitate the interconversion of B into A upon neutralization of the radical cation generally by electron capture. The second case likewise facilitates the energetically uphill transformation of A into B because the relative stability of the neutral and cationic forms of these two species has been reversed. Depending on the structure of the ion in common, one can imagine the third case favoring either of the neutral species depending on whether the ion structurally more closely mimics species A or B, and so forms A or B on electron capture.

The third reason for the interest in radical cations is that they may have molecular structures that do not correspond to any precursor neutral molecule so far isolated. Should these ions be formed from more complicated, but better understood, neutrals of higher molecular weight and/or should these ions fragment into known 'pieces', there is the possibility of gaining a better understanding of the energetics of neutrals and ions alike. Similarly, 'gently' adding an electron to these ions allows for the possibility of forming a new and otherwise uncharacterized neutral.

A case where all three reasons converge is the simplest cyclopropanoid species, cyclopropane itself. While cyclopropane, of course, is not a cyclopropane with additional strain, many of the concepts discussed below are generally applicable. Presented numerically, removal of the least bound electron from cyclopropane 'costs' 9.86 eV[64,65], a quantity significantly lower than the 11.5 eV of its acyclic, saturated analog, propane (1 eV = 23.06 kcal mol^{-1}). It should be noted that the highest occupied molecular orbital of cyclopropane is doubly degenerate and that the ion must have an unequal number of electrons in this pair of orbitals. Thus the Jahn–Teller effect results in the cyclopropane radical cation having less than the three-fold symmetry of the neutral. Both semiempirical[66,67] and *ab initio*[68,69] quantum chemical calculations show isomeric radical cations, each having only two-fold symmetry with lower total energies. These have been

described[66] as a 'complex of ethylene and CH_2^+' and 'the radical cation of trimethylene'. Relaxing all symmetry constraints on the calculated molecular geometry seems to result in an even lower energy[68] corresponding to a scalene as opposed to an isosceles triangular shape (i.e. three as opposed to two unequal sides). However, because the energy difference of the more stable of the two with two-fold symmetry and of these asymmetric structures is less than 1 kcal mol^{-1}, only the more symmetric species will be discussed in this chapter. Indeed, zero-point energy corrections may prove ultimately necessary and possibly even alter the relative stabilities. A possibly related case is that of CH_5^+ with regard to the relative orientation of the CH_3 and H_2 fragments (see Ref. 70).)

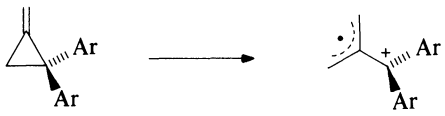
Both of the above isosceles species are consistent with the rather facile loss of CH_2^+ from photo-, electron or gas phase chemi-ionized cyclopropane[64]. In particular, cyclopropane radical cation reacts with NH_3, PH_3 and AsH_3 (generally EH_3) to form neutral ethylene and the corresponding $CH_2EH_3^+$ ions. These reactions have an efficiency comparable to those forming EH_4^+ and C_3H_5, in which ring-opening to allyl radical, has accompanied proton transfer. Evidence[64] by Lias and Buckley has been given that shows that not all the allyl radicals arise from rearrangement from initially formed cyclopropyl radicals. These authors additionally showed that the cyclopropane radical cation itself rearranges to propene radical cation with a barrier of between 30 and 37 kcal mol^{-1}, a value ca. half of that found earlier for the neutral cyclopropane[71].

One of the simplifying features of the parent cyclopropane is that all three C–C bonds are equivalent and that only one type of group or substituent is attached to the ring. Hexafluorocyclopropane is the only other compound with that feature that is also thermochemically well characterized. Despite significant differences between H and F and thus unavoidable major changes arising from perfluorination, these two species have significantly related ion chemistry. Hexafluorocyclopropane radical cation also undergoes a Jahn–Teller distortion and complete separation of the $C_2F_4^+$ and CF_2 fragments is achieved at rather low energies. (No reaction of $C_3F_6^+$ with any nucleophile has been reported and so it is not obvious whether CF_2^+ can be transferred.) Furthermore, while the barrier for isomerization of the neutral hexafluorocyclopropane into perfluoropropylene is at least 38 kcal mol^{-1}, this barrier is significantly reduced to at most 8 kcal mol^{-1} in the case of the radical cation[8].

In the case of cyclopropane it was shown that both the neutral and radical cations are well understood. Both the neutral[72] and ion forms are comparatively well understood in the additionally strained methylenecyclopropane and its ring-opened form, trimethylenemethane. In this case it is additionally known that it takes more energy to ionize methylenecyclopropane, 9.57 eV, than it does to ionize its acyclic analog, isobutene, 9.21 eV. In principle, methylenecyclopropane can be ionized either by loss of a π electron from the double bond or of a σ electron from the ring. That the vertical and adiabatic ionization potentials are so close for both species (i.e. a sharp ionization onset) strongly suggests loss of a π electron in both cases. It does not appear unreasonable for the radical cation of methylenecyclopropane formed by loss of a σ electron from the ring to ring-open to form the radical cation of trimethylenemethane. In the simplest picture of the latter, after all, there are three equivalent allylic carbons to delocalize both the unpaired electron and the positive charge. The suggested equivalence, however, is thwarted because of the Jahn–Teller effect. The resultant distortion divides the three carbons into two sets: one with two carbons and the other with one carbon. We also know that one set will bear the spin and the other the charge. Even with such comparably low symmetry the radical cation should enjoy considerable stability.

Intuitively, suitable substituents will favor placing the spin on one set and the charge on the other. Indeed, solution phase, chemi-ionization via a photoexcited quinone of gem-diaryl-substituted methylenecyclopropane results[73] in two, non-interconverting, different radical cations. For the 2,2-derivatives (**11**) the electron is lost from the ring. This results in

ring-opening (equation 21) to form a perpendicular trimethylenemethane derivative (**12**) while for 4,4-derivatives (**13**) the preferred loss of a π electron (equation 22) results in what may be called a 1-(diarylcarbenio)cyclopropyl radical (**14**).



(21)

(**11**) (**12**)

(22)

(**13**) (**14**)

Likewise, the radical cations of hetero-analogs of methylenecyclopropanes are expected to have two forms. However, almost nothing is known about them except that electron impact studies have derived an ionization potential of 9.1 eV for cyclopropanone. Intuitively, it seems likely that ring-opening to form oxyallyl cation should accompany ionization, although spontaneous rearrangement to form the radical cation of CH_2CHCHO or even a higher energy process resulting in decarbonylation to form $C_2H_4^+$ cannot be precluded. Photoelectron spectroscopy on cyclopropanones is seemingly limited to that of the *trans*-1,2-di-*t*-butyl derivative[74], for which loss of a non-bonding lone pair electron on oxygen in a vertical ionization process was demonstrated. The absence of a published spectrum, however, precludes our deducing either the adiabatic ionization potential or a π ionization potential with which to make comparisons with methylenecyclopropanes.

Surprisingly little is known about the energetics of the recently prepared, seemingly aromatic, methylenecyclopropene and its derivatives. (See Chapter 24 by Billups and Moorehead.) While experimental data are lacking, *ab initio* calculations[75] at the 6-31G* level show that the most stable neutral C_4H_4 isomer is the long known vinylacetylene and that methylenecyclopropene is some 24 kcal mol^{-1} less stable.

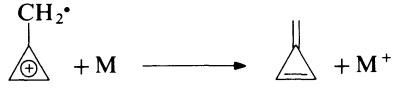
Data on the radical cations are much more definitive because the parent is well established as a fragment formed by the photoionization of benzene and its isomers, and its hetero derivatives such as pyridine and the three diazines. (This ion, its formation and thermochemistry, is reviewed in Ref. 76.) Unequivocally, the most stable $C_4H_4^+$ isomer is the radical cation of methylenecyclopropene. This last species is perhaps more explicitly and sensibly described as the $-CH_2^{\cdot}$ derivative of cyclopropenium cation and so renamed (cyclopropenio)methyl radical (**15**). From these studies, the heat of formation of this

(**15**)

radical cation is indirectly, but accurately known to be 289 kcal mol^{-1}, ca. 5 kcal mol^{-1} lower than that of vinylacetylene. If radical ion thermochemistry is available and reliable, why are data lacking on the neutrals? After all, a direct measurement of the ionization

potential of methylenecyclopropene would provide the heat of formation of the neutral. The authors eagerly await the results of this study[77]. Until it is performed, both the ionization potential and heat of formation of methylenecyclopropene must be deduced using non-empirical and/or indirect methods such as those discussed above.

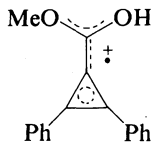
It might appear that the related measurement of the electron affinity of the $C_4H_4^+$ radical cation would be equally useful. However, one cannot expect simply 'dumping' an electron into a radical cation from a neutral molecule M to proceed without complication or ambiguity. That is, the seemingly simple electron transfer reaction (23) has conceptual



(15) (8) (23)

complications. Polar neutrals are well known to catalyze the gas phase isomerization of cations[78]. The gas phase isomerization of neutrals is expected to be analogously catalyzed by suitable cations, a result amply precedented in solution. Indeed, the above reaction, choosing M to be a suitable aromatic hydrocarbon with low ionization potential, does not yield methylenecyclopropene but rather its acyclic isomers, vinylacetylene or butatriene[79]. One should not be too surprised or disappointed because since isomerization is expected to generally accompany ionization of these acyclic hydrocarbons, microscopic reversibility then forces the ring-opening of the radical cation of methylenecyclopropene upon the addition of an electron.

There is one substituted methylenecyclopropene for which the radical cation is well understood: the 2,3-diphenyl, 4-hydroxy, 4-methoxy derivative (**16**). This ion is not formed by 1-electron oxidation or chemi-ionization from the methylenecyclopropene. Instead it arises from rearrangement of its tautomer, methyl 2,3-diphenylcyclopropene-1-carboxylate (**17**) in protic media[80]. This represents another example of reversal of stability



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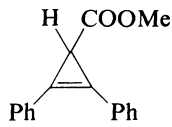


(17)

for the isomeric neutral and their derived radical cations. While the carbomethoxy group may be expected to destabilize the neutral cyclopropene because it is a π-withdrawing substituent, it should have an even greater destabilizing effect on the radical cation. The hydroxy and methoxy groups presumably stabilize the methylenecyclopropene radical cation because the two oxygen functionalities stabilize both the radical and cationic features. However, as they are π-donating substituents, they have the opposite electronic behavior to that which will stabilize the neutral methylenecyclopropene. There is, however, insufficient stabilization to allow for the isolation or spectroscopic characterization of the radical cation as it too readily undergoes a cycloaddition reaction with 9,10-dicyanoanthracene radical anion, the byproduct of the photochemical oxidation–reduction reaction from which it was derived. The related reaction of methyl 2,3-diphenylcyclopropene-1-carboxylate with other 1-electron oxidants is thus expected to be of interest to those studying radical ions and strained molecules alike.

Knowledge of the energetics of (c-$C_3H_2^+$)-$CH_2^\cdot$ (**15**) gives information relevant to those of other cyclopropene derivatives. If one accepts the above experimentally determined heat of formation of $C_4H_4^+$, the theoretical energy difference of vinylacetylene and methylenecyclopropene, and an ill-defined experimentally derived heat of formation of vinylacetylene[81], the ionization potential of methylenecyclopropene is indirectly deduced to be 8.2 eV. This value is meaningfully compared to the 9.5 eV directly measured as the ionization potential of cyclopropenone. The derived 1.3 eV difference is comparable to the 1.1 eV difference for the antiaromatic cyclopentadienone (with a vertical value of 9.5 eV) and non-aromatic methylenecyclopentadiene (i.e. fulvene, with an IP of 8.4 eV).

Data on few substituted species are available. Monomethylation decreases the ionization potential from 9.47 to 9.15 eV, a change somewhat comparable to that for the acyclic analogs of CH_2=CHCHO, MeCH=CHCHO and CH_2=C (Me)CHO, 10.13, 9.75 and 9.92 eV. Neither the considerable strain nor the significant aromaticity in cyclopropenones, as shown by the earlier discussed thermochemistry of diphenylcyclopropenone, seem to have any effect on the ionization potential. As befits a compound with two benzene rings, the ionization potential of diphenylcyclopropenone is 8.1 eV. While comparison with (*Z*)-PhCH=C (Ph)CHO would be interesting, there are no data on the latter species.

The comparison of the ionization potentials of identically substituted cyclopropenones, cyclopropenes and cyclopropanes is interesting, if not yet particularly informative to date. The ionization potentials of cyclopropane, cyclopropene and cyclopropenone are much closer, 9.86, 9.67 and 9.47 eV, than for their diphenyl derivatives. Diphenylcyclopropene has an adiabatic ionization potential of 7.45 eV while those of the *cis* and *trans* isomers of 1,2-diphenylcyclopropane (**18**) are 8.20 and 8.05 eV respectively. These latter values for the saturated species correspond to ring-opening to 1,3-diphenylprop-1-yl-3-ium (**19**) (equation 24) a result corroborated by both experiment via solution phase chemiionization[82,83] and *ab initio* calculations on the analogous divinylcyclopropane[69]. (The

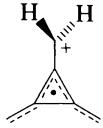
(18) (19) (24)

two* notation is taken to mean that the species has one cationic and radical center.) The low ionization potentials corresponding to the formation of ring-opened products does not prove that either isomer of 1,2-diphenylcyclopropane has additional strain either because of phenyl–phenyl repulsion or any through-bond destabilization. One can approximate the heat of formation of a 'normal' 1,2-diphenylcyclopropane by adding twice that for phenylcyclopropane and subtracting off that of cyclopropane. So doing results in a net ca. 1 kcal mol^{-1} stabilization of the *trans* isomer and comparable destabilization of the *cis* isomer for the disubstituted compounds. (Strictly speaking the experimental data are for the liquid mono- and diphenyl cyclopropanes and for gaseous parent cyclopropane. The heats of vaporization of the three phenylcyclopropanes were estimated by using rule 1 of Ref. 84, a simple one-parameter approach generally accurate to $\pm$ 1.5 kcal mol^{-1}).

Related to the methylenecyclopropene story, and a similarly instructive study involves $C_4H_4^+$ and deals with the photoionization and electron impact induced fragmentation[85] of [3]-radialene (**20**). Like other C_6H_6 species, such as the aforementioned fulvene, the following ionic fragments were observed: $C_6H_5^+$, $C_4H_4^+$, $C_3H_3^+$ and at considerably higher energy, $C_2H_2^+$. (The associated neutral fragments were presumably H, C_2H_2, C_3H_3 and C_4H_4.) From the known thermochemistry of various ionic and neutral hydrocarbon fragments, the heat of formation of this neutral C_6H_6 isomer was derived to be

(20)

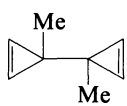
95(±3) kcal mol^{-1}. There is no other experimental number on this or any other radialene to challenge this value, and quantum chemically determined values presented in Ref. 85 range rather uselessly from 73 to 233 kcal mol^{-1}. Despite the fact that low temperature matrix studies[86] document the existence of a Jahn–Teller distorted *c*-$(CCH_2)_3^+$ radical cation (**21**), the reviewers feel uneasy about the suggested heat of formation of [3]-radialene because the fragment ion $C_4H_4^+$ was suggested to be the radical cation of butatriene, not the more stable ion derived from methylenecyclopropene, and the fragment ion $C_2H_2^+$ was suggested to be the radical cation of vinylidene, not the more stable ion derived from acetylene.



(21)

The above discussions of fulvene, [3]-radialene, and their derived ions quite naturally lead to a discussion of the other cyclopropyl-ring-containing C_6H_6 isomers and their ions. The first isomer of C_6H_6 to be discussed here is 3,3′-bicyclopropenyl. Both *ab initio* calculations on the parent[51, 52] and substituted[52] species and experiments on a collection of judiciously chosen substituted derivatives[52, 87] show a strong coupling of the π bonds in the two cyclopropene rings with each other via the C–C σ bond that joins the rings. Should one electron be removed from that sigma bond, the resulting species may be described as the radical cation of the 3,3′-bicyclopropenyl. It may also be described as the dimer ion formed from one each of the cyclopropenyl cation and radical. Indeed, such a dimer ion has been spectroscopically observed[88] via pulse radiolysis (electron bombardment) of trimethylcyclopropenium ions in solution. A catalytic cycle that converted the radical cation of hexamethyl-3,3′-bicyclopropenyl into that of hexamethylbenzene was also observed. The analogous solution phase reduction of tri-*t*-butylcyclopropenium ion produced only the cyclopropenyl radical: no evidence for any neutral or cationic form of $(c\text{-}(t\text{-Bu}))_6$ was observed. Chemical[89] and electrochemical[90] reduction of triphenylcyclopropenium ion resulted in formation of hexaphenyl 3,3′-bicyclopropenyl, while the reduction of diphenylcyclopropenium ion under the latter set of conditions produced what is undoubtedly the most stable tetraphenylbenzene, the 1,2,4,5-isomer.

One may alternatively remove an electron from one of the π bonds of 3,3′-bicyclopropenyl, although in fact this process produces the same radical cation as before because of extensive through-bond interactions. Solution phase, photoexcited quinone-induced chemi-ionization[91] of 3,3′-dimethyl-3,3′-bicyclopropenyl (**22**) results in the



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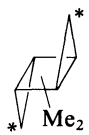
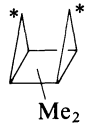


(23)

radical cations of *o*- and *m*-xylene where the proposed mechanism involves the radical cations of various dimethylbenzvalenes (*vide infra*) and a dimethyl derivative of *anti*-tricyclo[3.1.0.0^{2,4}]hexane-1-yl-4-ium (**23**) for which the two *s are a cationic and radical center. In any case, the mechanism for rearrangement of neutral 3,3'-dimethyl-3,3'-bicyclopropenyl is assuredly different—the literature mechanism involves vinylcarbenes and Dewar benzenes on route to a different isomer distribution of xylenes[92]. Similarly, there are substituted cyclopropenes (e.g. the 'semi-acyclic' bicyclopropenyl derivatives, 3-allylcyclopropenes) that chemi-ionize to produce final products consistent with the intermediacy of the radical cations of vinylcarbenes[93].

Interestingly, the *syn* isomer of the above-mentioned tricyclo[3.1.0.0^{2,4}]hexane-1-yl-4-ium (**24**) may be described alternatively as a radical cation derived from the highly strained cyclopropanoid dimethyltriprismane (**25**). As such, besides a preliminary and still ill-defined chemi-ionization result on the parent compound[94], the above represents the sole

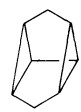


(**24**)

(**25**)

example of ion chemistry of any triprismane known to the authors. By contrast, the ion chemistry of the likewise highly strained homotriprismanes is better understood, although there is no apparent pattern. That is, the adiabatic ionization potentials of monohomotriprismane (quadricyclane, **26**), bishomotriprismane (**27**) and trishomotriprismane (triasterane **28**) are 7.8 eV, 8.4 eV and 8.2 eV. Interestingly, the radical cation of quadricyclane

(**26**)

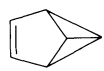


(**27**)

(**28**)

rearranges and relaxes within nanoseconds, i.e. thousands of vibrations, to form that of norbornadiene[95] but that is another story.

The last C_6H_6 isomer and its derivatives to be discussed here is benzvalene (**29**). In this case, the neutral and cation are thermochemically characterized. Benzvalene is a highly

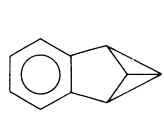


(**29**)

strained species that may be recognized to be simultaneously a vinylcyclopropane, a bicyclobutane, a bicyclo[2.1.1]hexene and a bicyclo[3.1.0]hexene. Reaction calorimetric studies of the liquid phase isomerization of benzvalene to benzene[96] show it to lie some 67 kcal mol^{-1} higher in energy than benzene. Using the experimental heat of vaporization of benzene and that estimated for 'an average C_6 hydrocarbon' (employing rule 1 of Ref. 84 again), it is ascertained that gaseous benzvalene is likewise ca. 67 kcal mol^{-1} less stable than gaseous benzene.

In that the various 'components' of benzvalene all have rather low ionization potentials, it is not surprising that benzvalene does also. The experimental value, 8.10 eV, is some 25 kcal mol^{-1} lower than that of benzene. Benzvalene radical cation is thus less stable than benzene radical cation by $67 - 25 = 42$ kcal mol^{-1}. However, like the neutral benzvalene, benzvalene radical cation does not immediately isomerize in the gas phase[97]. Little is known about the ion chemistry of substituted benzvalenes. The *in situ* produced[91] cation radicals of 3,4-dimethylbenzvalene resulted in initial isomerization to that of the 5,6-isomer prior to eventually forming the cation radicals of *o*- and *m*-xylene. The radical ion chemistry of benzvalene is thus conceptually inseparable from that of yet other cyclopropane with additional strain.

In trying to make sense out of these diverse data on whether electron loss lessens strain, the simplest regularity arises from the observation of whether the electron is removed from the predominantly olefin or bicyclobutane fragment. This interesting ambiguity is resolved in the case of benzvalene to be from the former as shown by gas phase photo-[97] and solution phase chemi-ionization[98]. Moreover, to the extent that the electron is taken from a 2-butene type orbital, one may expect that ionization of naphthvalene (**30**) and 'pleiavalene' (**31**) will also be from the π-system because the ionization potentials of *o*-xylene and 1,8-dimethylnaphthalene are still lower. This is confirmed experimentally[98].



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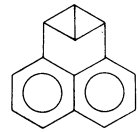
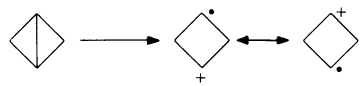


(**31**)

Clearly in the absence of such an available π electron it is necessary to ionize a σ electron. Such is the case for 'saturatedly substituted' bicyclobutanes where the 1,3- or interbridge-head bond is ionized and severely weakened. The simplest case, of course, is bicyclobutane itself and its methyl derivatives. Experiment and theory both show[99] that methyl substitution at the 1 and/or 3 bridgehead positions causes a much larger decrease in the ionization potential than the analogous substitution at the 2- and/or 4-positions. This is only compatible with the assumption that the highest occupied molecular orbital is mostly composed of atomic orbitals of the bridgehead carbons and only negligibly delocalized along the four $-CH_2-CH<$ bonds. Equivalently, in a valence bond sense, one may say that ionization in the parent bicyclobutane (**32**) results in a secondary radical and a secondary cation, cyclobutane-1-yl-3-ium (**33**, equation 25). Species **33** is quite obviously quantum mechanically inseparable from its resonance structure cyclobutane-1-ium-3-yl (**34**). Since



(**32**) (**33**) (**34**) (25)

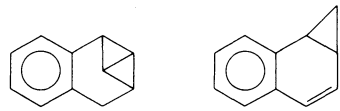
the existence of resonance is always stabilizing, the bicyclobutane radical cation is thus additionally stabilized over the neutral. Substitution on the 2- and 4-carbons does not change this description as a 'secondary, secondary' cyclobutane-1-yl-3-ium ion and little additional stabilization is suggested. However, substitution on the 1-carbon results in a secondary radical and tertiary cation, and so considerable stabilization is expected. For example, this bridgehead ionization is also found in the 'saturatedly substituted' cases of

dihydrobenzvalene (**35**), (2,4-(1,2-dimethylene)bicyclobutane)[98] and 2,4-(1,3-trimethylene)bicyclobutane (**36**) (Refs 98, 100, 101). The reaction chemistry of the radical

(**35**) (**36**)

cation of the latter species is consonant with this initial step and then followed by (1) 'a cyclobutyl–cyclopropylcarbinyl type rearrangement [to] . . . an edge-weakened bicyclobutane'[98] resulting eventually in norcarene (bicyclo[4.1.0]hept-2-ene), (2) addition of a nucleophile (HO^-, MeO^-, NC^- [100,101]) or (3) formal dimerization of the neutral hydrocarbon to form (*E*)-1,2-di(cyclohexen-3-yl)ethylenes[101].

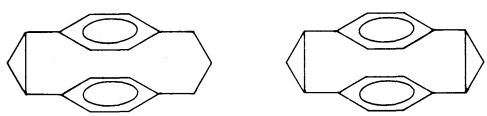
Despite π bonds in benzohomobenzvalene (**37**) its radical cation chemistry mimics that of the saturated cases and the radical cation of benzonorcarene (**38**) is observed as an intermediate[98]. It is not at all surprising that the above rapid rearrangements occur for the radical cations. Actually it is the 'longevity' of the neutrals, given their considerable strain energies, that is noteworthy.



(**37**) (**38**)

Having written at some length about the ionization of bicyclobutanes, what can be said about other bicyclo[n.1.0]alkanes? The answer is surprisingly little. There are several competing effects that do not depend monotonically on the total number of carbons. The first is the strain energy released upon ring-opening to form either the cyclo[$n+3$]alkane-1-yl-3-ium or cyclo[$n+2$]alkane-1-ium-2-carbinyl radical cations. The second is the relative stability of cycloalkyl radicals and cations. Experimentally, the following numbers are found: $n = 0$, i.e. cyclopropene, 9.7 eV; $n = 1$, 8.7 eV; $n = 2$, 8.7 eV; $n = 4$, 9.0 eV; $n = 6$ (*trans*), 9.4 eV. Only vertical ionization potential data are available for the $n = 6$ case, a situation that only exacerbates the seeming lack of trend of ionization potential vs. n.

The last aspect of general bicycloalkane radical cation chemistry we discuss relates to the di- and tetradehydro[3.3]paracyclophanes[102], **39** and **40**, that may be said to be derivatives of bicyclo[3.1.0]hexane and tricyclo[3.1.0.$0^{2,4}$]hexane formed by 'stretching'[103]. For the radical cations of both the di- and tetradehydro cyclophanes, both the unpaired electron and the charge in the radical cation are delocalized over both rings and all of the benzylic carbons.



(**39**) (**40**)

Electrochemical oxidation was largely ignored in the above discussion save for the ease of ionization of the variously methylated bicyclobutanes. This was a conscious omission because this approach is generally simultaneously quantitatively accurate and qualitatively

ambiguous. While photoionization and photoelectron spectroscopic studies can give the molecular ionization potential directly, chemi-ionization studies can only provided an upper bound. Electrochemical oxidation also gives information about the molecular ionization potential but is complicated by the ambiguities of (1) the differential solvation energies of the ion and of the neutral parent and (2) the differential binding on the electrode of the ion and the neutral. It is also not altogether obvious what molecular geometry changes occur on an electrode surface and so it is not clear whether the electron transfer corresponds to that of the gas phase vertical or adiabatic ionization process, or to some other process. These ambiguities, however, are not apparent in the electrochemical oxidation of strained species[104]. For a set of polycyclic hydrocarbons containing three- and/or four-membered rings, the half-wave oxidation potential was shown to correlate with the adiabatic gas phase ionization potential IP_a by equation 26:

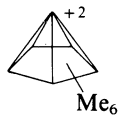
$$IP_a = 1.28E_{1/2} + 6.25 \text{ (eV)} \tag{26}$$

with a correlation coefficient of $r = 0.988$. The large intercept is consistent with considerable condensed phase stabilization of the cation by differential solvation. The slope of 1.28, however, is not so simply explained, and indeed it may be noted that our conceptually more 'simple' equation 27:

$$IP_a = E_{1/2} + 6.71 \text{ (eV)} \tag{27}$$

has a standard deviation only 0.02 eV poorer than the more complicated equation 26 given in the literature. No qualitative or quantitative relationship, however, exists between the relative ionization potentials and strain energies of isomers.

This section on single electron ionization to form cation radicals is logically concluded by a brief discussion of the possibility of ionization to form dications and of their chemistry. Though quantitation is absent, there are three pieces of indirect data that relate to this latter class of cations. The first is the existence and the high stability[105] of the pyramidal carbocation, $[C(Me)]_6^{+2}$ (**41**). This species may be viewed as formally the dication of hexamethylbenzvalene where the five-fold symmetry in the dication is thwarted by Jahn–Teller effects for the neutral and radical cation forms. No coproportionation reaction of this dication and any neutral benzvalene has been reported to our knowledge.



(**41**)

The second is the existence of the dication of variously substituted cyclobutadienes[106]. *Ab initio* quantum chemical calculations[107] indicate that at least the parent dication, **42**, is significantly non-planar (**43**). This is suggestive of some 1,3-bonding although one would hesitate to describe this ion as bicyclobutane-1,3-diium (**44**) (*vide infra*). Perhaps even more reluctantly, one may describe this species as the dication of tetrahedrane (**45**) where both electrons have been removed from the same C–C bond. Indeed, the closed shell (or singlet) dication of tetrahedrane will lack strict tetrahedral symmetry because of unequal orbital occupancies and resulting Jahn-Teller distortion[107]. It is presumably this C–C bond

(**42**) (**43**) (**44**) (**45**)

stretching and resulting planarization that also accompanies the monocation that facilitates 'immediate' isomerization of tetra-*t*-butyl tetrahedrane radical cation into the ion of the isomeric cyclobutadiene[108].

The third returns the reader to chemi-ionization of cyclopropane derivatives with excited state electron acceptors. In the particular, it has been observed[109] that oxidation of 1,6-dimethylbicyclo[4.1.0]hept-3-ene (**46**) and [4.4.1]propella-2,6-diene (**47**) result in 2,6-dimethylcycloheptatriene (**48**) and 1,6-methano[10]annulene (**49**) (equations 28 and 29 respectively). The former compound is conceptually the deprotonation product of the dication wherein the C–C bond between the bridgehead carbons has been totally depleted of electrons. In this case, however, the dication is not expected to be as stable as in the above pyramidal or cyclobutadiene cases and indeed, the product is seemingly not formed via the dication route. The methanoannulene likewise does not arise from the tetracation of its precursor. Rather, proton and electron transfer reactions involving 'merely' radical cations proceed to remove hydrogens sequentially.

(46) (48) (28)

(47) (49) (29)

VI. WHEN IS A CYCLOPROPANE NOT A CYCLOPROPANE?

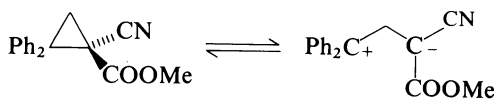
This concluding section will discuss those cases in which a suitably substituted cyclopropane is so strained that it is on the edge of spontaneous rearrangement and/or unimolecular decomposition. One can imagine such self-destruction arising from the cleavage of one, two or three skeletal C–C bonds. What we wish to discuss are first and foremost a cyclopropane derivative that is relatively unstable compared to a product formed by the breaking of *only* one or two or all three of the skeletal bonds with no other bond simultaneously being broken or formed during this process. This author-imposed limitation of precluding other bonds being simultaneously involved thereby prevents the inclusion in this section of nearly *all* existent cyclopropanes. After all cyclopropane itself is thermodynamically unstable relative to its acyclic isomer propene that is formally formed from it by cleavage of one C–C bond and the migration of one hydrogen.

A second limitation of this chapter is that only cases where the barrier for interconversion of the cyclopropane into another species is small or even absent are being considered. For example, the cyclopropyl cation is thermodynamically unstable with respect to the breaking of one skeletal C–C bond to form its corresponding acyclic, allyl isomer. Indeed this cation is so fragile, i.e. susceptible to this rearrangement, that it has only recently been unambiguously seen experimentally in free form by a method which utilized photoionization of the *in situ* formed gaseous cyclopropyl radical[110]. Other experiments such as proton transfer to cyclopropene have yielded instead the 'hot' allyl cation, e.g. some partially ring-opened and/or rotationally excited species. The energy difference of the

cyclopropyl and allyl cations[110] is ca. 30 kcal mol^{-1}, a quantity somewhat larger than the 27 kcal mol^{-1} for the much more kinetically stable radicals[111]. This relative thermodynamic stability is no doubt shared by the kinetically stable pair of isomeric cyclopropyl and allyl anions—although direct thermochemical data are absent, the strain energy of cyclopropyl anion has been calculated to be *only* ca. 4 kcal mol^{-1} less than for the neutral cyclopropane[31]. As such, only cyclopropyl cation, and not cyclopropyl radical or anion qualifies in the current context as a cyclopropane on its way to being no longer a cyclopropane.

The first, and simplest, class of cases to be discussed is that for which the breaking of one bond suffices to convert a cyclopropane into a non-cyclopropane. This process may be labelled a molecular rearrangement, although valence tautomerism (valence isomerism), molecular distortion and 'bond-stretch isomerism'[112] are perhaps more accurate descriptions. Earlier discussed studies in this chapter include the aforementioned cyclopropyl–allyl cation isomerization, the substituent dependent equilibrium between neutral tropylidenes and norcaradienes and the energetics of numerous radical cations such as those of 1,2-diphenylcyclopropane and bicyclobutane where the alternative descriptions 1,3-diphenylpropane-1-yl-3-ium and cyclobutane-1-yl-3-ium may be explicitly recalled. What follows is a systematic, albeit incomplete, collection of examples of other one bond cleavage reactions that make a cyclopropane not necessarily a cyclopropane. (This discussion is inseparable from that of long C–C bonds in neutral, but otherwise general organic compounds, for which the reader is addressed to a recent review, Ref. 113.)

Starting with formally 'one going-on zero' ring systems, i.e. species for which one-bond cleavage converts a one-ring species into one that is acyclic, there is the above-mentioned radical cation of 1,2-diphenylcyclopropane which is 'missing' a bonding electron. There are also cyclopropyl cation, methylenecyclopropane and cyclopropanone, and their derivatives, in which a sp^2 carbon destabilizes the ring while allylic resonance simultaneously provides stabilization for the acyclic or open form. An example of a neutral, 'saturated' cyclopropane that readily ring-opens[114] to form a zwitterion stabilized on both sides is the 1-cyano, 1-carbomethoxy, 2,2-diphenyl derivative, **50** (equation 30), although it must be noted that careful rate/solvent/product analyses are imperative to distinguish the intermediacy of zwitterions as opposed to biradicals[115, 116]. (Indeed, the authors admit that this disclaimer constitutes the sole discussion of the interesting and important



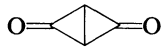
(30)

(50)

intermediate 1,3-trimethylene and its derivatives.) While perhaps more in the province of photochemical than thermochemical reactions, high accuracy quantum chemical calculations[117] on the 1,1-difluoro and 1,1,3,3-tetrafluoro derivatives of methylenecyclopropane show these species to be but ca. 4 kcal mol^{-1} more stable than the acyclic, triplet, diradical forms. By contrast, at the same calculational level, these authors showed that there is a 45 kcal mol^{-1} energy difference for the parent, singlet, closed-shell hydrocarbon.

Proceeding to 'two rings going-on one' class, neutral derivatives of bicyclobutane with the two non-bridgehead carbons replaced by sp^2 hybridized or trigonally coordinated atoms show self-destructive behavior for related reasons (see Chapter 19 by Hoz for a review of bicyclobutanes). Our 'suicidal' species include the hypothetical bicyclobutane-2,4-dione (**51**)[118, 119] and its 1,3-disubstituted derivatives, recognized as 'squaraines' (**52**)[120]. The theoretical analysis of the parent diketo compound suggests the non-planar form also lacks the C–C bond. The 2,4-dibora compounds are experimentally known to be

non-planar[121] but formal theoretical analysis[119] suggest the bridgehead C–C bond is likewise absent. More precisely, the hypothetical 2,4-parent[122] diborabicyclobutane (1*H*,3*H*-1,3-diborete), **53** and the experimentally realized[121] 1,3-di-*t*-butyl-2,4-bis(dimethylamino) derivative (**54**) show the same non-planar structural feature. While the



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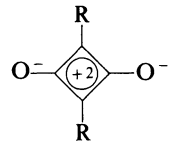

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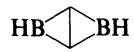

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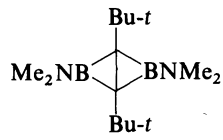
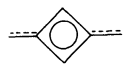


(54)

comparison of trigonally coordinated carbon and boron is interesting, and even generally instructive, any further discussion will be omitted here in the name of brevity. The study of heteroderivatives of cyclopropanes could amply fill another chapter, if not volume, and many such species would qualify in a corresponding discussion of 'rings that are not rings'. (Simple examples include acyclic carboxylate anions, and the 1,3-dipoles, nitrile oxides, nitro compounds and ozone that could then be compared to the corresponding cyclic isomers, dioxiranides, oxazirines, dioxaziridines and trioxirane.)

Recently what would appear to be the conceptually simplest such bicyclobutane 'two rings going-on one' species—which may alternatively be named 2,4-dimethylenecyclobutane-1,3-diyl; 2,4-dimethylene-1,3-cyclobutadiyl; 1,3-dimethylene-cyclobutadiene and 2,4-dimethylenebicyclobutane (**55**)—has been experimentally prepared[123]. An elegant nine step synthesis commencing with benzvalene and culminating



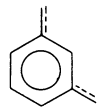
(55)

with a low temperature photolysis yielded this novel hydrocarbon. An EPR measurement accompanying the final photolysis step has been interpreted as suggesting a triplet ground state as opposed to the closed shell singlets found for the diketo and dibora species discussed above. While again the cyclopropane substructure is so strained as to have cleaved the C–C bond that so defined it, the relative energy of the corresponding singlet and of the formal 2,4-dimethylenebicyclobutane remain unknown and so simple comparison is thwarted.

The above examples of 'two rings going-on one' dealt with bicyclo[1.1.0]butane derivatives. Proceeding to derivatives of larger rings, one may naturally consider bicyclo[2.1.0]pentane and its derivatives. Considerably less stable than the neutral bicyclo[2.1.0]pentene (the parent hydrocarbon[124] has a half-life of 4 hours at 34°C) are the derivatives of bicyclo[2.1.0]pentene-5-yl cation. Depending on the substituents, these bicyclopentyl cations are unstable with respect to immediate ring-opening to form

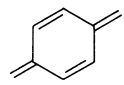
cyclopentadienyl cations or 'folding' to form (square) pyramidal cations[105]. While geometrically these square pyramids have four triangular faces, it is doubtful that any reader would consider these species as having four cyclopropane rings. Counting cyclopropane rings for pyramidal carbocations is rather moot as is the case of other non-classical ions such as the norbornenyl-tricyclyl cation, where the resonance structures correspond to no and one cyclopropane ring respectively. The reader may recall the related ambiguity in the cyclopropylcarbinyl cation where the earlier, alternative names[125] 'bicyclobutonium ion' and 'tricyclobutonium ion' might suggest two or even three cyclopropane rings at least in a formal, bookkeeping sense. Names corresponding to other related structures, e.g. cyclobutyl and homoallyl cation, suggest the absence of any cyclopropane ring at all.

The next example of 'two rings going-on one' deals with the interrelated chemistry of bicyclo[3.1.0]hexane and cyclohexane derivatives. One important interrelationship involves general 'non-Kekulé' species[126], an extensive but still largely unexplored class of neutral organic compounds. These species are characterized by an inadequate number of double bonds compared to their more conventional isomers. (The reader may thus recognize the non-Kekulé label as applicable for the compounds in the earlier 2,4-dimethylenebicyclobutane–1,3-dimethylenecyclobutadiene discussion because, however drawn, the latter has but two double bonds while the isomeric C_6H_6 species, 3,4-dimethylenecyclobutene, fulvene and benzene each have three.) The question of whether the ground state of a given non-Kekulé species is a triplet or singlet, and whether the latter is a biradical or a zwitterion is endemic to this class of compounds (see the discussion in Ref. 127). Likewise intrinsic to these species is a comparison with cyclopropane-containing isomers. Quantitative comparison of these non-Kekulé species with normal isomers either with Kekulé structures or with cyclopropane rings is almost unexplored. One of the few meaningful examples is *m*-xylylene (**56**). Gas phase ion chemistry[128] shows *m*-xylylene to have a heat of formation of at least 77 kcal mol^{-1} while the *o*- and *p*-isomers, **57** and **58**,



(**56**)

(**57**)



(**58**)

have the much lower value of 55 and 56 kcal mol^{-1} respectively. A simple estimate[103] of the heat of formation of the *m*-isomer was made assuming no interaction of the two $-CH_2$ carbons (equation 31):

$$m\text{-}C_6H_4(CH_2)_2 = 2C_6H_5CH_2 - C_6H_6 \tag{31}$$

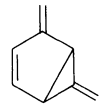
The derived value, 78 kcal mol^{-1}, is seen to be compatible with that found experimentally. Since the assumption of non-interaction of the two $-CH_2$ groups appears valid, a triplet ground state may be suggested for *m*-xylylene. By contrast, the heats of formation for the isomeric *o*-and *p*-xylylenes are much lower than those found using formally related estimates (equations 32 and 33).

$$o\text{-}C_6H_4(CH_2)_2 = 2C_6H_5CH_2 - C_6H_6 \tag{32}$$

$$p\text{-}C_6H_4(CH_2)_2 = 2C_6H_5CH_2 - C_6H_6 \tag{33}$$

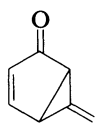
This difference of heats of formation of the xylylenes as experimentally found and estimated correctly suggests significant interaction between the two CH_2 groups. The 'new', admittedly fallacious, numbers are in fact, most applicable to the lowest lying, excited triplet states of *o*- and *p*-xylylene. The heats of formation of these excited states may

be directly obtained from adding those of the ground state singlets to the appropriate singlet-triplet energy difference: the literature values are 81 kcal mol^{-1} for both isomers in good agreement with our simplest of models[129]. Using analogies to more normal species and Benson group increments, an estimate of 90 kcal mol^{-1} for the heat of formation of the isomeric singlet cyclopropane-containing compound, 4,6-dimethylene bicyclo[3.1.0]hex-2-ene (**59**), has been made[130]. This value is sufficiently higher than the

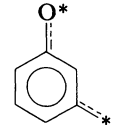


(**59**)

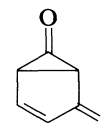
experimental heat of formation of *m*-$C_6H_4(CH_2)_2$ that it seems safe to discount the bicyclic species as that observed in the ion chemistry experiments. The triplet ground state assignment is corroborated by both experiment and a new 'semi-empirical' calculational approach to the energetics of these compounds[127]. Interestingly, the mono-oxygen analog has been shown to exist in the cyclopropanoid 6-methylenebicyclo[3.1.0]hex-2-en-4-one (**60**) and both the singlet and triplet *m*-benzoquinomethane (**61**) forms[130–132], each with their own individualized chemical reactions. From the observations that α,β-unsaturated ketones have more resonance energy than conjugated dienes and that cyclopropanone is more strained than methylenecyclopropane, it may be deduced that the above singlet is more stable than the other, classical, cyclopropane isomer, 4-methylenebicyclo[3.1.0]hex-2-en-6-one (**62**). Indeed, no direct evidence exists for this last isomer although pyrolysis of



(**60**)



(**61**)



(**62**)

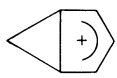
the '6-methylene- . . . -4-one' isomer yields fulvene and CO, a reaction suggestive of sequential thermal isomerization and decarbonylation[132].

The question of 'two rings going-on one' is also seminal to the study of homoaromaticity. For *n* odd, the set of $[(CH)_nCH_2]^+$ ions demonstrate a delicate balance between mono and bicyclic structures (see Ref. 133 and numerous references cited therein to both the experimental and theoretical literature). In the case of $n = 3$, one can imagine a planar cyclobutenyl cation (**63**) and a markedly non-planar, highly puckered bicyclobutyl cation (**64**). Both calculational theory on the parent and experiment on derivatives show the latter geometry to be preferred. However, as in the case of the other purported bicyclobutane derivatives characterized by the 2,4-carbons trigonally coordinated that were discussed earlier in this section, formal theory shows there is no 1,3-bond. The ion is not homoaromatic and there is no cyclopropane ring. In the case of $n = 5$,

(**63**)

(**64**)

bicyclo[3.1.0]hexenyl cation (**65**) and cyclohexadienyl cation (**66**, benzenonium ion), both isomers are stable and have separate identities and reactivities. That is, one isomer is a cyclopropane derivative while the other is not. The $n = 7$ case follows the behavior of

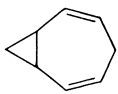


(**65**)

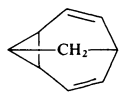
(**66**)

neither lower homolog. One can clearly write structures corresponding to both cyclooctatrienyl and bicyclo[5.1.0]octatrienyl cations. Formal theory shows the ion seemingly to be neither: there is not a full 1,3-bond or cyclopropane ring. This ion is homoaromatic.

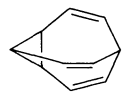
If homoaromaticity in cations has been hard to define and delineate, documentation for neutral species has proven even more elusive. It would *thus* appear that even if a cyclopropane is experimentally reactive, unstable and fragile, at least counting the number of cyclopropane rings in a given molecular structure is generally quite straightforward despite non-Kekulé species constituting an important class of potential exceptions. As such, we note that tropylidene derivatives have no cyclopropane rings, while the isomeric norcaradienes have one each. Which is more stable depends on the substituent attached. While this may be experimentally a subtle question as to the presence or absence of a cyclopropane ring in the 'real' compound, both isomers have well-defined structural descriptions. Likewise, homotropylidene (**67**), semibullvalene (**4**), barbaralane (**68**) and bullvalene (**69**) each have one cyclopropane ring. Substitution often modulates the barriers



(**67**)



(**68**)

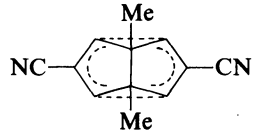


(**69**)

to isomerization and/or automerization (degenerate isomerization) so as to 'freeze' the Cope rearrangement. The isomer interconversion may then be experimentally thwarted. For example, recall that the monofluoro derivative of bullvalene has the fluorine atom predominantly at the bridgehead while the monochloro and bromo derivatives have the heavier halogen located on a vinylic position—in no case is the halogen atom on the cyclopropane preferred[134].

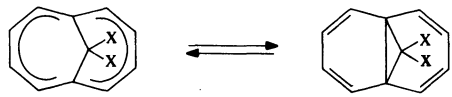
Suitable substitution can also decrease the isomerization barrier. As predicted using essentially qualitative theory[135], the semibullvalene system is markedly susceptible to such modulation. For example[136], 3,7-dicyano substitution increases the barrier in 1,5-dimethylsemibullvalene from 6 to 10 kcal mol^{-1} while 2,6-dicyano substitution decreases the barrier to ca. 4 kcal mol^{-1}. (Strictly speaking, the comparison is being made between data on the isomeric dimethyldicyano semibullvalenes and that of the parent hydrocarbon[137].) Recently, it has been shown[138] that 1,5-dimethyl-2,6-dicyanosemibullvalene has a thermally accessible isomer that corresponds to a delocalized, homoaromatic structure (**70**), i.e. the cyclopropane has disappeared! It is perhaps not so obvious when a cyclopropane is a cyclopropane.

Semibullvalenes and related fluxional hydrocarbons are not the only tricyclic species with such ambiguity as to the presence of cyclopropanes. Propellanes (see Chapters 1 and 20 by Wiberg and Ginsburg respectively) provide numerous examples of the 'three rings going-on two' species. The whole question of the relative stability of small



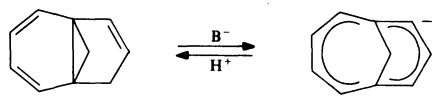
(70)

(l.m.n)propellanes and the isomeric bicyclo(l.m.n)alkane bridgehead diradicals is expressible in these terms. A somewhat simpler example for neutral species is the methano-[10] annulene (**49**)–[4.4.1]propellatetraene (**71**) equilibrium (equation 34) for which



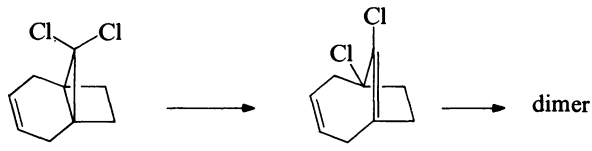
(49) (71) (34)

substituent effects have been probed. While the parent species prefers the former[139], the 1-bridge disubstituted dimethyl compound prefers the latter[140] (i.e. **71**, X = Me). Analogous halogen substitution also affects this equilibrium: the difluoro compound is more stable as the former and the dichloro and dibromo compounds as the latter[141]. The [4.3.1]propellatriene system shows a related equilibrium[142] wherein the neutral, parent propellane species (**72**) is more stable with its cyclopropane ring intact than the opened form while its conjugate base exists as the methano[9]annulenide (**73**, equation 35). The [4.2.1]propellene system provides an interesting example, albeit one that violates our self-imposed



(72) (73) (35)

limitation of not wishing to break any bond save that in the C–C skeleton. Proceeding anyway, the 7,7-dichloro species[143], **74**, simultaneously breaks a C–Cl and cyclopropane C–C bond in a rapid ionization process (that is spontaneous even in non-polar medium) and results in isomerization (equation 36) of the propellene to an anti-Bredt, bicyclo[4.2.1]nonadiêne (**75**). By contrast, the corresponding 7,7-dibromopropellene solvolyzes rather slowly[144].

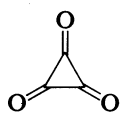


(74) (75) (36)

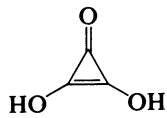
Examples of comparatively 'suicidal' behavior of cyclopropanes associated with the cleavage of two C–C bonds are found in the cases of hexafluorocyclopropane (neutral and

especially radical cation) and diphenylcyclopropenone where CF_2 and CO are lost. 1,1-Difluorocyclopropane is likewise a cyclopropane on the way of not being a cyclopropane. Another case is cyclopropanone for which decarbonylation is not only entropically favored but also enthalpically—using the heat of formation of cyclopropanone[145] of 3.8 kcal mol^{-1}, the reaction to form ethylene + CO is exothermic by 18 kcal mol^{-1}. The thermal stability of cyclopropanone is a tribute to the conservation of orbital symmetry. The thermal instability of cyclopropanone, however, is not due solely to the cyclopropane ring even when accentuated by the additional strain due to the presence of an sp^2 hybridized carbon and an electronegative substituent. This instability is inherent in general, 'normal' ketones. For example, a corresponding acyclic species, gaseous acetone, is but 5 kcal mol^{-1} lower in energy than ethane + CO. Viewing this decarbonylation process in equilibrium, i.e., explicitly considering entropy and free energy, shows that even liquid acetone is on the unstable side of the reaction.

The authors know of no 'real' molecule for which the last case of cleavage of all three bonds is experimentally realized. To so fragment requires both considerable strain in the parent cyclopropane and considerable stabilization in the product. However, it is highly probable that cyclopropane-1,2,3-trione (**76**) would qualify. Neglecting any additional strain because of adjacent sp^2 hybridized carbons and any electrostatic destabilization because of adjacent keto groups, the heat of formation of cyclopropane-1,2,3-trione may be estimated to be that of three cyclopropanones minus two cyclopropanes or -14 kcal mol^{-1}. By contrast, the heat of formation of three carbon monoxide molecules is -81 kcal mol^{-1}. One should thus not be surprised that dihydroxycyclopropenone (deltic acid, **77**) is relatively unstable[146] although admittedly no study designed to explicitly



(**76**)



(**77**)

oxidize this species to the above trione is known to the authors. It is anticipated that 3,3-difluorocyclopropane-1,2-dione and the mono-, di- and triimines of cyclopropane-1,2,3-trione will likewise fragment into three pieces. Perhaps the most interesting case devised by the authors involves the diimines because they should chelate numerous metals and 'indulge' simultaneously in the stabilization of unusual valences for the metals and of the ligand. Contrariwise, in their -2 oxidation state, the diimines are now derivatives of the 'normal' 2,3-diaminocyclopropenones for which extra stabilization as for other vinylogous amides may be expected. Oxidation–reduction chemistry of these complexes should show some interesting surprises and the authors look forward to the results of such studies.

VII. ACKNOWLEDGEMENTS

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CHAPTER **19**

Bicyclo[1.1.0]butane

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I. INTRODUCTION

Although bicyclobutane is not known to be a natural product or a cornerstone in any synthesis of commercial value, this fascinating molecule has attracted enormous attention from the scientific community. The chemistry of bicyclobutane officially started in 1959 with the formation of its first derivative by Wiberg and Ciula[1] (previous claims for the successful preparation of bicyclobutane derivatives have been shown to be in error[1]).

As can be inferred from the annual rate of publications on this subject, the number of bicyclobutane studies proliferated rapidly during the late 1960s and the early 1970s. After a relatively calm period in the mid-seventies, the interest in this molecule regained momentum.

Most of the basic chemistry of bicyclobutane was uncovered in the exciting competitive atmosphere of the small-ring compound era. Since then, the 'temperature' of the subject has somewhat decreased. An indication to this can be obtained from a plot of the ratio of fast publications (such as communications and letters) to full papers per year, as shown in Figure 1. It is interesting to note that while this ratio declines with time, the total number of papers published on bicyclobutane increases (the noticeable peak in the early seventies which distorts the relatively steady trends results from the impact of transition metal chemistry on bicyclobutane research). Naturally, the current interest in bicyclobutane has somewhat shifted from basic studies towards more specific theoretical and experimental issues aimed at uncovering the secrets of this interesting molecule.

The latest full review on bicyclobutane appeared in 1968[2]. Since then, the chemistry of bicyclobutane has been reviewed only briefly, and mainly with respect to specific topics such as polymerization[3], transition metals[4] and within the general context of strained ring

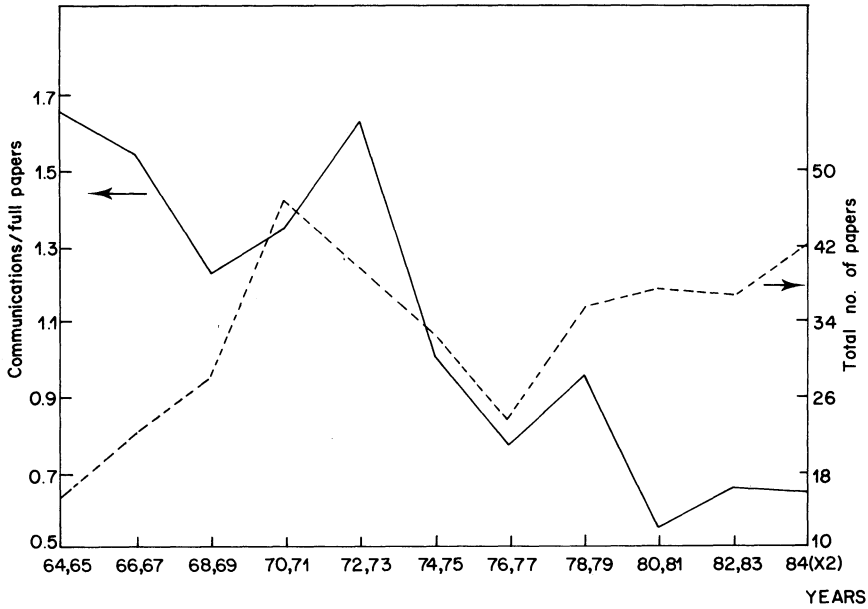


FIGURE 1 Trends in the publication of bicyclobutane related articles from 1964 to 1985 (solid line: ratio of communications to full papers; dashed line: total number of articles)

compounds[5]. Therefore, in this chapter the coverage of the material will be somewhat more extensive than is usually found in this series*.

II. STRUCTURE AND BONDING

A. Structure

Four different experimental techniques were employed in attempts to elucidate the structure of bicyclobutane. Haller and Srinivasan[6] obtained some structural information from the analysis of partially resolved infrared vibration–rotation bands. However, this method is not expected to give results of high accuracy, especially since some of the fundamental parameters has to be assumed. Meiboom and Snyder[7] used NMR measurements in liquid crystals for structure determination. One limitation of this method is that only ratios of internuclear distances rather than absolute values can be determined. Also, the authors point out that their results should not be considered as final since corrections for vibration were not made[7]. The other two methods successfully employed were electron diffraction[8] and microwave spectroscopy[9,10]. The structural parameters obtained by these methods are collected in Table 1.

Of the four sets of data given in this table, the last two are probably of higher accuracy. It is therefore not surprising that both of these methods give for the majority of the

* The literature covered in this chapter includes the beginning of 1985 when this chapter was drafted. The author wishes to thank the many researchers in this field who furnished him with hitherto unpublished results.

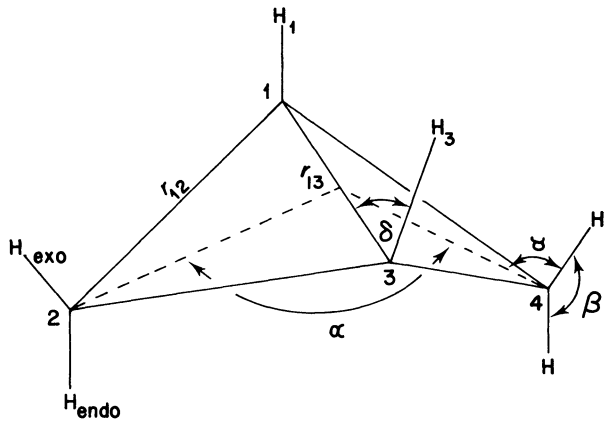


FIGURE 2 Structure of bicyclobutane

TABLE 1. Structural parameters of bicyclobutane[a,b]

Method	α	β	γ	δ	C(1)–C(2)	C(1)–C(3)	C(1)–H(1)	C(2)–H_{exo}	C(2)–H_{endo}
Vibrational spectra[c]	126	118[d]	121	163	1.53[d]	1.54	1.08[d]	1.08[d]	1.08[d]
NMR[e]	120.2	110.2	126.3	128.0	1.507[d]	1.507	1.142	1.194	1.167
Electron diffraction[f]	122.8	111.6	~122	125.5	1.507	1.502	1.108	~1.106	~1.106
Microwave[g]	122.7	115.6	122.9	128.4	1.498	1.497	1.071	1.093	1.093

[a] Data refer to notations in Figure 2.
[b] Angles are given in degrees and bond lengths in Angstroms.
[c] Ref. 6.
[d] Assumed.
[e] Ref. 7.
[f] Ref. 8.
[g] Refs 9, 10.

geometrical parameters results which are identical within experimental error. It is worth pointing out that quantum mechanical calculations performed after 1969 usually employ the geometry obtained by the microwave method (*ab initio* optimized structures usually give results that are compatible with the experimental data with the noticeable exception of a shorter calculated central bond[11-13])

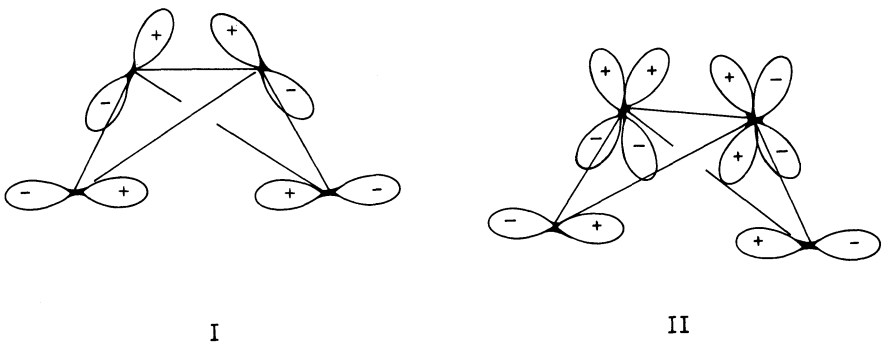
Two important geometrical features of bicyclobutane are revealed by all four methods:

(1) the molecule is highly puckered (C_{2v} symmetry) with an interflap angle of ca. 123°; and
(2) in spite of the differences in the electronic structure as well as in the chemical reactivity between the central and the lateral C–C bonds, they are both of practically the same length.

Another feature which is not immediately recognized is that the bridgehead carbons acquire an inverted geometry, namely all four bonds of each carbon are contained in a single hemisphere.

B. Bonding

Two Walsh-type descriptions for the electronic structure of bicyclobutane were suggested by Pomerantz and Abrahamson[14]. Both models introduce π character into the peripheral and the central bonds employing sp^2 hybridization for the methylene groups. The two models differ in the hybridization of the bridgehead carbons. It is sp^2 in the first model and sp in the second (see Figure 3).



I II

FIGURE 3 Walsh orbitals representations of bicyclobutane

MO treatments at all levels, from extended Huckel[15] and CNDO[16] to *ab initio* calculations[17], show that the central bond is composed mainly of atomic p orbitals on the bridgehead carbons. According to the classic paper of Newton and Schulman[17], the C(1)–C(3) bond is formed from hybrid orbitals with 96% p character (or $sp^{24.3}$) as compared to cyclopropane where the percentage of p character is 86. Analysis of the localized MO employed in this study reveals also that the hybridization in the C(1)–C(2) bond is sp^3 on C(1) and $sp^{5.1}$ on C(2). Obviously, as a result of the extensive use made of the atomic p orbitals in the construction of the C–C bonds, the C–H bond of the bridgehead carbon contains a higher degree of s character ($sp^{1.58}$).

The marked correlation between hybridization and the ^{13}C–H coupling constants[18,19] has provided another mean to estimate the amount of the s character in the bridgehead C–H bond. According to this correlation, J_{C-H} increases linearly with the s character in the bond. Figeys and coworkers[20] formulated this in a linear equation (equation 1)

$$J_{C-H} = 6.91(\%s) - 72.39 \text{ Hz} \quad (1)$$

Implementing the value of 205 for the bridgehead C–H coupling constant[21] in equation 1 results in 40% s character of the carbon hybride in this bond. This is in a good agreement with the value obtained by theoretical calculations although it should be pointed out that the calculated percent of the s character in the bond depends to some extent on the basis set used in the calculation.

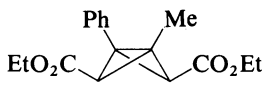
Similar correlation exists also for $J_{C_A-C_B}$. This is exemplified by equation 2[22]

$$J_{cc} = 0.062(\%s_A)(\%s_B) - 10.2 \text{ Hz} \quad (2)$$

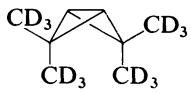
Before continuing the discussion, a brief comment on the factors governing the coupling constants between two bonded atoms is in order. According to work of Ramsey[23], spin–spin coupling results from three different coupling mechanisms. These are orbital-dipole, spin-dipole and Fermi-contact interactions. The success of equations such as equation 2 is due to the fact that in most cases the Fermi-contact interaction is the dominant effect. To a first approximation, the magnitude of this effect is linearly correlated with the product of the s fraction on each of the two coupled atoms. Thus for example, using a similar relation and assuming 15% s character on the methylene carbon, Grant and coworkers[24] calculated the hybridization of the bridgehead carbon to be sp^3 in its lateral bonds. This value is in an excellent agreement with the one reported by Newton and Schulman[17] ($sp^{2.97}$).

Surprisingly, INDO[17,22] as well as *ab initio*[25,26] coupled Hartree–Fock calculations, predicted a negative value for J_{cc} of the central bond. The semi-empirical method gives a somewhat higher (absolute) value for each of the three coupling mechanisms showing also that all the mechanisms including the Fermi-contact, contribute to the overall negative value of the coupling constant.

Experimentally, negative values were indeed observed confirming the theoretically expected trend. However, these values range from −5.4 for **1**[27] to −17.49 Hz for **2**[28] (and probably −16 for bicyclobutanecarbonitrile[29,30] and −8.8 for **3**[31], where the negative sign was not proven).



(1)

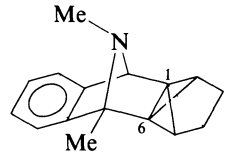


(2)

(3)

In light of the previous discussion, it is clear that the percentage of s character in the central bond of bicyclobutane cannot be safely deduced from the observed coupling constant of the two bridgehead carbons. An attempt to circumvent this problem was made by Pomerantz and Hillanbrand[29] who calculated the amount of the s character used in the other bonds of C(3) in bicyclobutanecarbonitrile. Since the total s character around the bridgehead carbon is 1.0, the amount of s character left for the central bond can be calculated and was found to be 10.8% ($sp^{8.26}$).

In the preceding discussion it was assumed that the central bond of bicyclobutane is 'normal'. In other words, the bonding is due to some electron density between the two bridgehead carbons. However, it is worth pointing out that in one case this assumption has been challenged. Thus, electron-density difference maps obtained for **4** show that although the distance between C(1) and C(6) is not unusual for a C–C bond (1.574 Å), no residual electron density was observed between these two carbon atoms[32]. However, whatever its physical meaning is, this seems to be a unique case since none of the many theoretical



(4)

analyses performed on bicyclobutane or its derivatives revealed this feature. Moreover, it has been recently shown that the electron density along the C(2)–C(3) bond in butane is similar to that of the central bond in bicyclobutane[12].

C. Deformation Densities

Bond strain in small-ring molecules generally shows itself in a displacement of deformation density peaks outside of the ring. As a consequence of the curvature of the C–C bond paths in strained molecules, the charge density is not distributed so as to maximize the force of attraction between the nuclei. As a result of this effect, the bonds are weakened in spite of the fact that in general they exhibit intranuclear distances shorter than normal bonds.

The deformation of the C–C bonds in bicyclobutane has long been recognized[33]. In addition to the outward displacement which is reported to be larger for the central bond than for the lateral ones[34,35], Eisenstein and Hirshfeld[35] found that the side bonds are also displaced out of the ring plan as a result of a non-bonded repulsion between the two methylene groups. This is in contradistinction to an earlier report of Newton and Schulman[17] who, using a minimal basis set, observed the out-of-plane bending to be downward into the region between the two cyclopropane planes.

D. The Nature of the Central Bond

After establishing that the central bond is composed almost solely of p orbitals on each of the two carbons, it remains to establish the orientation of these orbitals with respect to each other. The two possible extremes are: σ overlap in which the two orbitals are oriented towards each other or π bonding for which they are parallel. Extended Huckel calculations performed by Yonezawa and coworkers[15] assign a large π character to this bond. On the other hand, a 5:1 ratio of p-σ to p-π bonding was reported on the basis of *ab initio* calculations[36]. Other *ab initio* calculations (STO-3G) suggest that the bond is bent outward but differ as to the extent (45°[37] and 30.8°[17]). Thus one may conclude that the central bond of bicyclobutane, although formally a σ bond, contains appreciable π character.

Since most of the quantum mechanical calculations performed on bicyclobutane were closed shell calculations, they were incapable of revealing whether a biradical character exists in its central bond. Recently a calculation made by Schleyer and coworkers[13] on the GVB/3-21G optimized geometry of bicyclobutane, assigned a 4% biradical character to this bond.

E. The HOMO of Bicyclobutane

In general, for unstrained and unsubstituted alkanes, the HOMO is associated with a C–H bond. However, none of the *ab initio* calculations reported in this chapter suggests that in the case of bicyclobutane, the HOMO is associated with any other bond than the

central one. Experimental verification of this was obtained by Gassman and coworkers who measured the half wave oxidation potentials as a function of the number and location of methyl substitution[38]. Theoretical investigation of other substituted bicyclobutanes showed that in all cases the lowest ionization potential is always obtained for the bridgehead substituted bicyclobutane[39].

Interestingly, the energy of the HOMO of bicyclobutane was found to be higher than that of ethylene[36]. The first electronic transition in bicyclobutane, namely the π–π^* (HOMO–LUMO) transition, is lower in energy than in ethylene[40,41]. The position of the onset of the first band in its photoelectron spectrum suggests an adiabatic ionization energy of 8.70 eV[42].

The HOMO, the LUMO and their nearest orbitals as calculated by Wiberg and coworkers[41] are given in Figure 4.

F. Strain in Bicyclobutane

Bicyclobutane is a highly strained molecule. Quantitative estimation of its strain energy depends on the group increments used. With a value of 51.9 kcal mol^{-1} for its ΔH_f[43], the strain energy estimations span a range from 63.9 to 66.5 kcal mol^{-1}. The first value is obtained from the Franklin[44] and the latter from the Schleyer[45] group increments.

MINDO[46] as well as STO-3G[47] calculations were found to give good agreement with the experimental values. Further theoretical analysis by Dill and coworkers[47] has shown that substitution, especially at the bridgehead carbon, can significantly affect the strain energy of the molecule. Thus for example, a carbonitrile group at the bridgehead position was found to reduce the strain energy by 6 kcal mol^{-1}[47].

Bicyclobutane is unique in that it does not obey the strain additivity rule of small-ring bicyclo[n.m.0]alkanes. For example, the strain energy of bicyclo[2.1.0]pentane, using the Franklin group increment is 53.6 kcal mol^{-1}. This should be compared to the sum of the strain energies in cyclobutane (26.4) and cyclopropane (27.6 kcal mol^{-1}). Yet, the sum of two cyclopropanes (55.2 kcal mol^{-1}) is ca. 9 kcal mol^{-1} lower than that of bicyclobutane.

In this respect the nearly identical strain energies of cyclobutane and cyclopropane are somewhat surprising. One of the possible origins of this phenomenon is probably the two 1–3 interactions in cyclobutane. Such an interaction was estimated by Bauld and coworkers[48] to induce a destabilizing effect of 10–16 kcal mol^{-1}. The gap between the expected and observed strain energies of bicyclobutane is suggested to be due to a single repulsive interaction of this type as shown in (**5**) between the two methylene carbons[48].

(**5**)

G. Molecular Distortions

The following discussion relates to the effect induced by a change of one geometrical parameter in bicyclobutane on some of the other parameters. Attention to this field was drawn by the stimulating work of Irngartinger and Lukas[49] who found that an interesting relationship exists between the interflap angle α and the C(1)–C(3) distance. This result which was based on crystallographic studies was successfully simulated by *ab initio* calculations[50] over a flap angle range of 90–130°. The calculations show that as α increases, the central bond is lengthened, the side bond shortens (to a smaller extent) and the bridgehead hydrogens move inward (diminishing δ).

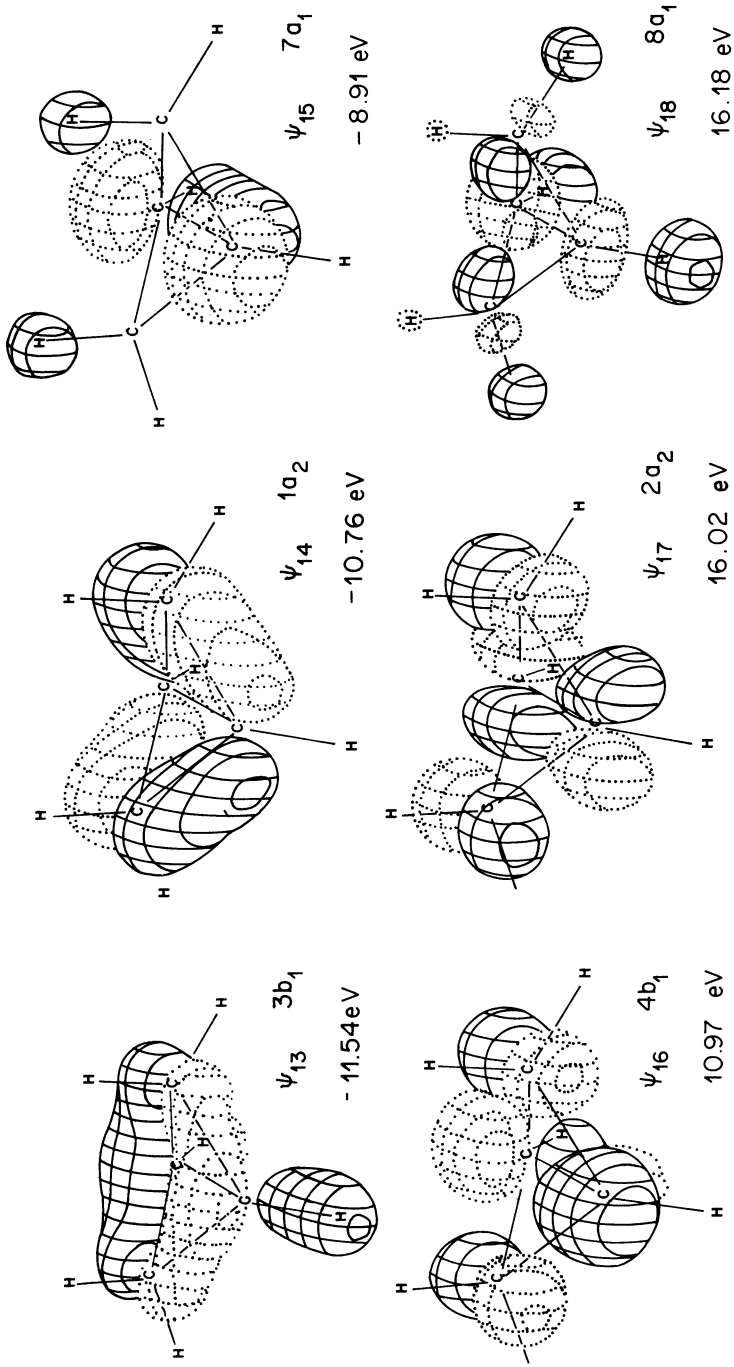
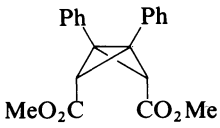
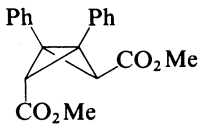


FIGURE 4 Some *ab initio* derived orbitals of bicyclobutane

X-ray analysis of the three isomers of 1,3-diphenyl-2,4-bis(carbomethoxy)bicyclobutane (**6**), namely, the *endo–endo* (**6a**), the *endo–exo* (**6b**) and the *exo–exo* (**6c**) isomers, show the same trends[51]. As α decreases (127.2, 121.2 and 113.4°) r_{13} also decreases (1.558, 1.498 and 1.455 Å respectively). These motions are coupled with an inward motion of the two phenyl



(6a)



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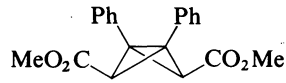


(6c)

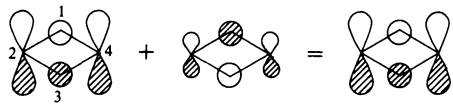
rings. Theoretical studies of this effect on the parent bicyclobutane were also performed by the same group[51]. These extend over interflap angles from 99 to 180°. The calculations show that around $\alpha = 150°$ the inward motion of the bridgehead hydrogens is stopped and a reversal of this motion takes place. At an interflap angle of 180°, the molecule still belongs to the C_{2v} (and not the D_{2n}) symmetry group since the two bridgehead hydrogens are above the carbon plane by approximately 30°. Thus, during the course of the isomerization of the di-*endo* to the di-*exo* isomer[52], the bridgehead substituents move inward at the first stages and then, as expected, begin to move outward.

The inward movement of the bridgehead substituents coupled with the changes in α and C(1)–C(3) bond length was also realized by Eisenstein and Hirshfeld[53]. Analyzing X-ray crystallographic data, they have also noted that the average bond length in each cyclopropane ring is fairly constant throughout the series (1.503 Å), supporting the principle of fixed total bonding[54, 55].

The relationships between the various structural parameters were quantitatively formulated by Allen[56] (equation 3).

$$r_{13} = 1.408 + 0.00224\alpha - 0.001447\delta \tag{3}$$

A theoretical explanation of the observed coupling between α and r_{13} was offered by Zil'berg and coworkers[57]. Using MOs (MINDO/3) for the planar bicyclobutane, they suggested that this effect results from a polarization interaction of an occupied orbital with a vacant one (equation 4). Upon puckering, this interaction not only strengthens the C(2)–C(4) 'bond', but also diminishes the antibonding interaction along the central bond.



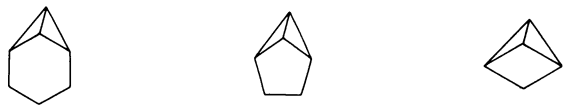
(4)

More interesting, however, is the inward motion of the bridgehead substituents as C(1)–C(3) distance is increased. An inward movement of a substituent on C(1) (as in structure **A**) from its normal position affects the p orbital utilized for the C(1)–C(3) bonding in two ways. The first is a better alignment toward a σ overlap with its counterpart on C(3). The second effect is due to an admixture of an s character into the hybrid orbital resulting in a 'squeezing out' of the orbital from the bonding zone. An outward motion (as in structure **B**) will cause the reversal of these effects (at least over short distances). These two outcomes have opposite effects on the binding property of this orbital. In the inward movement for example, the preferred σ orientation is opposed by a smaller overlap effect due to the diminished size of the orbital in the bonding zone. The balance of these two effects determines the tilt angle δ of the bridgehead substituent.

(A) (B)

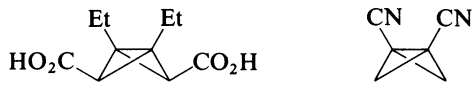
At relatively large distances where there is only weak bonding (if at all) between the two carbons, these considerations probably become less important and secondary interactions take over.

In addition, the following points are of interest. As α and C(1)–C(3) are decreased, the central bond becomes stronger and at a certain point, the HOMO even moves to the side bond[38,51]. Experimental support for this trend is obtained from PES studies[58], which show that the ionization potentials of **7** and **8** are 8.72 and 9.43 eV respectively. Another interesting observation is the increase in the J_{C-H} for the bridgehead hydrogen as the interflap angle is diminished. This was observed for a series of compounds in which C(2) and C(4) are bridged by three, two and one methylene units[59,60] (**7**, **8** and **9** respectively). This change corresponds to an overall increase of only 2% in the s character upon going from **7** to **9**, and may be interpreted as being a result of an outward movement (toward



(7) (8) (9)

planarity with the cyclopropane ring) of the bridgehead hydrogens, which is expected to increase the s character in the C–H bond. It should be pointed out that the molecular framework of bicyclobutane displays a relatively very high degree of flexibility. Thus for example, as noted by Eisenstein and Hirshfeld[53], the three compounds **10**, bicyclobutane itself and **11**, all lacking *endo* substituents, have an interflap angle of 112.8, 121.7 and 126.4° respectively.



(10) (11)

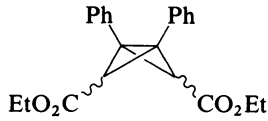
It appears, therefore, that the bicyclobutane skeleton must be quite easily deformable by intra- or intermolecular forces such as those existing within a crystal.

Theoretical analyses also confirm this point[17,51]. It was found for example, that a 5° change in δ around the equilibrium point changes the energy by less than 1 kcal mol^{-1}. Similarly, a change of α by 10°, results in an increase in energy of only ca. 5 kcal mol^{-1} [17]. In light of the relative flatness of the potential surface of bicyclobutane around the equilibrium position, other forces such as those exerted by the crystal lattice, can easily induce distortions which may cause deviations from the correlations observed.

H. Orbital Interactions with External Fragments

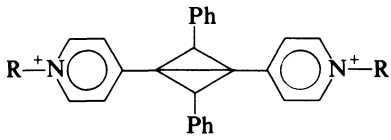
Due to the π character of the central bond in bicyclobutane it can interact with a bridgehead substituent in an allylic-like manner. This is reflected for example, in the ability to conjugate the two phenyl groups of **12**[61]. The UV spectrum of the *endo–endo* isomer of

12, shows λ_{max} at 270 nm ($\log \varepsilon = 4.0$). In the *exo–exo* isomer, where the two phenyl groups adopt a nearly 'bisected' conformation (from X-ray measurements[51]), and conjugation is therefore disrupted, λ_{max} is blue shifted to 223 nm ($\log \varepsilon = 4.12$)[61]. An alternative



(12)

suggestion[36] is that the absorption of the *endo–endo* isomer was due to a through space interaction of the two parallel phenyl groups which is disrupted by the *exo* carboxyl groups in the other isomer. However, it is doubtful if such an interaction can indeed exist since the distance of the two closest carbons of the phenyl groups in the *endo–endo* isomer is about 3.5 Å (estimated from X-ray data[5]). Similarly, the two pyridinium groups of **13** were found to be strongly conjugated via the central bond of bicyclobutane[62].



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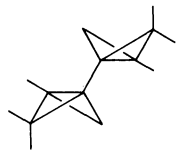
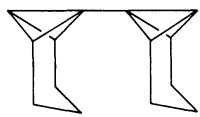


(14)

Another demonstration of conjugation effect on the UV spectrum was provided by the butadiene analog **14**. In this case, upon going from the 'monomer' to the conjugated 'dimer', a red shift was observed[63].

Butadiene-like conjugation was also manifested by Harnish and Szeimies[64] in the reaction of **15** with acids that gave a 1,4- rather than 1,2-addition.

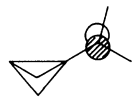


(15)

An impressive demonstration of the ability of the central bond of bicyclobutane to interact effectively with an allylic-like position was reported by Wiberg and coworkers[65]. They found that the solvolysis of 1-bicyclobutylcarbinyl *p*-nitrobenzoate, is at least 1000 times faster than that of the analogous cyclopropyl dérivative.

The ability to stabilize a carbocation at an allylic-like position, was theoretically reproduced by Greenberg[66], who compared (STO-3G) the difference in energy of the two conformations **16** and **17** of the bicyclobutylcarbinyl cation. Conformation **16**, in which

(16)

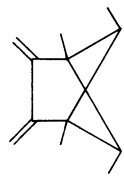


(17)

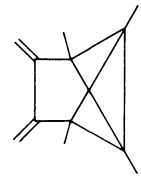
the empty orbital can overlap with the central bond, was calculated to be more stable by 32 kcal mol^{-1} than the bisected conformation **17**.

An intriguing result was obtained when the same calculation was performed on the anion. In this case, the differences between the overlapping and the bisected conformations amounted to only 3.5 kcal mol^{-1}, i.e. about one-ninth of the value calculated for the cation[66]. This could have been taken as an indication of the poor ability of the central bond to stabilize a neighboring negative charge. However, a more detailed study by Hoz and Levy, with a larger basis set and full optimization, has indicated that the small difference in the energies of the two conformations is not due to the inability of the central bond to stabilize the anion in conformation **16**, but rather to the ability of the molecule to stabilize the negative charge in the orthogonal conformation **17**[67]. In this conformation the doubly occupied orbital is stabilized by an interaction with an empty orbital composed of two σ^* orbitals of the side C–C bonds having the same symmetry.

Another type of interaction was revealed by the work of Capozzi and Hogeveen[68]. Studying the ability of the two dienes **18** and **19** to participate in Diels–Alder reactions, it was found that **18** reacts sluggishly with TCNE, requiring 20 hours at 55° for completion of the reaction. On the other hand, the reaction of **19** with TCNE proceeds in less than



(18)

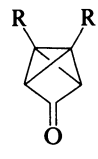


(19)

1 minute at room temperature. This was traced to an interaction of the bicyclobutane moiety with the π system of the diene as well as with the product olefin, which is absent in the cyclobutane bridged diene **18**[69–71].

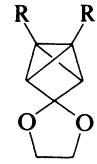
Theoretical and PES studies on benzvalene and other derivatives where aromatic rings bridge carbons 2 and 4 of bicyclobutane, have indeed confirmed these postulated interactions[72].

An interesting interaction exists between the bicyclobutane moiety and the carbonyl group in **20**. As a result of the presence of this group, the central bond is somewhat shortened[73]. This cannot be due to a change in the interflap angle since the analogous



(20)

R = CH_2OAc



(21)

compound **21**, has the same interflap angle and a longer central bond[74]. This interaction was confirmed by theoretical treatments[57,75].

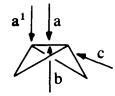
III. STRUCTURE AND BONDING EFFECTS ON REACTIVITY

The locus of reactivity of bicyclobutane is located primarily at its central bond which is also associated with the HOMO of the molecule. Its reactivity is in many respects similar to that

of olefins. The manifestation of this similarity in actual reactions will be discussed in detail in later sections of this chapter. In this section, we will focus on the theoretical aspects of the reactivity.

One of the major structural differences between bicyclobutane and an analogous olefin lies in the differing symmetries of the two systems. The former lacks the σ_h element which is typical of the latter. In other words, unlike ethylene, bicyclobutane has two unidentical faces above and below its central π-like bond. This necessarily leads to the question: which of the two faces is more reactive? Electrophilic reactions are a good vehicle for the analysis of this problem. As will be mentioned later, protonation of bicyclobutane can lead to products that may be regarded as resulting from attack on the central bond as well as on a side bond. Two theoretical studies were addressed to the interesting problem of the preferred direction for proton approach.

In 1970 Wiberg and Szeimies using CNDO calculations have examined five such possible directions[76]. Three of these approaches, a, b and c in **22**, are aimed towards cleavage of the central bond. Approach along d and e (cf. **23**) will result in the cleavage of a side bond. These calculations show that e (edge attack in the plane of the cyclopropane



(22)

(23)

ring) is preferred over d (perpendicular to this plane). An approach in the e direction is also favored over an approach along c which is in turn preferred over a and b. This is in accordance with the available information regarding cleavage of cyclopropanes. Three years later, using a minimal basis set, Lehn and Wipff repeated these calculations and, in contradistinction to Wiberg and Szeimies, found that an approach along c is favored by ca. 30 kcal mol^{-1} over e[77]. This conclusion is strongly supported by the fact that the HOMO of bicyclobutane is associated with the central bond (absent in cyclopropane) rather than with the side bonds. It should be pointed out, however, that these calculations suffer from two severe limitations. First, as was mentioned by the authors, in both cases, the geometry of the bicyclobutane was not continually reoptimized during the approach of the proton. Second, it is obvious that the calculations do not mimic reactions in the condensed phase. According to these calculations, the proton approach to the bicyclobutane is a barrierless process. It is only the stability of the resulting protonated bicyclobutane which serves as a criterion for the extent by which one mode of approach is favored over the other. In spite of these limitations, this method becomes somewhat more reliable when the energy differences between the various paths are relatively large as it is in these calculations.

Examination of the electronic structure of the central bond reveals that a back side approach (along c) is not entirely unexpected. Since the major constituent of this bond is an atomic p orbital, its spatial distribution on both sides of the bridgehead carbon should be similar. In fact, the slight inward pyramidalization of the bridgehead substituents may cause some asymmetry of the hybrid orbital (by admixing some s character into it), rendering its external side bulkier than the inner one. Hence, a better overlap between the entering electrophile and the HOMO will probably be achieved by an attack along the equatorial direction.

When activated by electron-withdrawing groups, bicyclobutane undergoes nucleophilic reactions similar to the Michael reactions observed in olefins[78]. Surprisingly, nucleophilic reactions also proceed from the equatorial direction. Using a 4-31G basis set, Hoz showed

that the back–side attack is the prefered mode for the approach of H^- to bicyclobutane[79]. Although in these calculations the geometry of bicyclobutane was not reoptimized at each step, the difference in energy for H^- at 1.5 Å from the bridgehead carbon between the equatorial (c) and axial (a′) approaches is about 60 kcal mol^{-1}. At shorter distances this difference rises steeply. It is interesting to note that since the positive end of the dipole resides above the molecule[9], electrostatic considerations will prefer, in the case of a charged nucleophile, an axial approach. However, it seems that the covalent interactions dominate in this case.

Thus, one may conclude that theoretical calculations as well as experimental results (see Sections V.A and V.C) suggest that both nucleophilic and electrophilic reactions occur predominantly from the back–side of the bicyclobutane molecule. These may result at least in part from the fact that both the HOMO and the LUMO reside heavily on this side of the molecule. In addition, due to the inverted geometry of the bridgehead carbons, the equatorial side is sterically more exposed than the axial one.

The similarity between bicyclobutane and olefins in the type of reactions they undergo is broken by a single marked exception. This is the Diels–Alder reaction which has not been observed in the bicyclobutane system. Although in some cases cycloadducts were obtained, it appears that these reactions occur by a two-step process rather than by a concerted mechanism (see Section V.B).

This unexpected observation was used by Schulman and Fisanick[36] to support their model for the electronic structure of the central bond. Since according to their model, the bond has only 20% π character, it is clear that the orbital is not properly oriented toward the incoming diene and therefore fails to partake in Diels–Alder reactions. It is highly likely that even if the central bond has a higher π character, as predicted by other models (see Section II.B), its reactivity as a dienophile is likely to be reduced greatly as compared to olefins. In addition, some steric inhibition to the approach of the diene will be caused by the two bridgehead substituents.

Although yet unproven, it is possible that reactions could occur by an approach of the reactant from above the central bond. Favored cases for such reactions will be bicyclobutanes with small interflap angle. As was previously mentioned, this distortion causes an outward displacement of the bridgehead substituents. Consequently the steric effect will be reduced while the π character will be enhanced. Both factors are expected to render bicyclobutane more prone to attack from the axial direction. It should be pointed out that calculations by Gassman and coworkers[51] have shown that at very small interflap angles, the HOMO is shifted to the side bonds (whereas the LUMO is not). This, if true, may cause a new type of chemistry which at this stage has not been proven to exist for bicyclobutane.

Another reactivity domain in bicyclobutane is the bridgehead proton. As can be predicted from the large s character of its bond to the bridgehead carbon, this proton is relatively highly acidic. As will be shown in Section V.I, this feature is often used to prepare certain bridgehead derivatives of bicyclobutane.

A rough correlation between the relative rates of deprotonation and the J_{C-H} for the bridgehead protons in the series **7**, **8** and **9**, was observed by Closs and Larrabee[59]. Taking the C–H coupling constant as a measure of the acidity of hydrocarbons, the acidity of the proton in bicyclobutane is expected to be between that of acetylene and ethylene (J_{C-H} values for acetylene, ethylene and bicyclobutane are 248, 156 and 205 Hz respectively).

In conclusion, the often invoked similarity between bicyclobutane and olefins is only partially correct. It is most likely that this similarity stems primarily from the following two features which are common to both systems: a high lying HOMO accompanied by low lying LUMO and a high p character with some π nature in the reactive bond. The differences, on the other hand, stem mainly from the different spatial arrangement of the hybrid orbitals comprising the HOMO. This is reflected in the relatively low π character of

the central bond in bicyclobutane (as compared to olefins) and the asymmetry of its two faces.

IV. SYNTHESIS

A thorough description and analysis of a synthetic method, should cover various aspects including availability of starting materials, yields, versatility, stereochemistry and mechanism of the reaction. In the case of bicyclo[1.1.0]butane, most of the synthetic routes were developed in the early 1960s and have already been reviewed by Wiberg[2] in 1968. The present review will therefore focus only on the crucial last step in which the bicyclobutane moiety is generated.

A. Classification

The reactions leading to bicyclobutane can be classified according to the bond(s) formed in the last step of the synthesis. According to this classification the reactions fall into two categories. In the first, a single bond is formed, be it a C–C side bond (case A) or the central bond (case B).

case A case B

The second category includes reactions in which the simultaneous formation of two carbon–carbon bonds completes the framework of the bicyclobutane moiety. For the sake of simplicity, carbene insertion reactions as well as some photochemical transformations are considered in this context as being concerted reactions[80].

Theoretically, there are four possible combination in which a pair of C–C bonds can be formed (cases C–F).

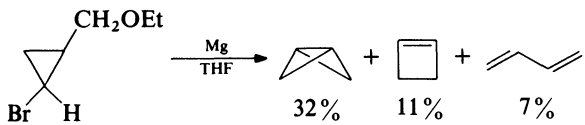
case C case D case E case F

B. Synthetic Routes

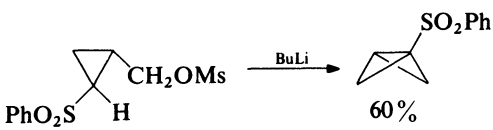
1. Case A

Starting with a cyclopropylcarbinyl system, ring-closure via formation of a side C–C bond in bicyclobutane can be affected by several processes.

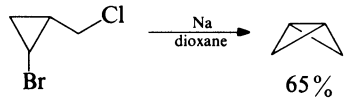
The following three examples demonstrate an ionic pathway.



(Ref. 81) (5)



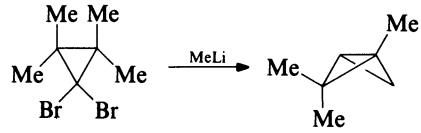
(Refs 82, 83) (6)



(Ref. 84) (7)

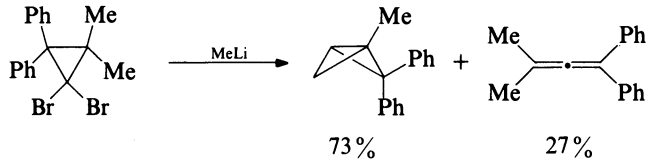
In these reactions the nucleophilic carbanion is produced either by deprotonation or by metal reduction of a C–halogen bond. It is interesting to note that, as in other cyclopropane formation reactions[85], even a sluggish nucleofuge such as EtO^- can be displaced in these intramolecular nucleophilic reactions (equation 5).

Most of the reactions where a side bond of bicyclobutane is formed involve the insertion of a carbenoid generated from a geminate dibromocyclopropane into a β-C–H bond. In some cases the yield of these reactions is almost quantitative (equation 8)[86,87].



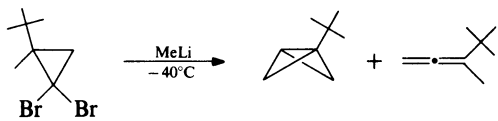
(8)

This carbenoid approach is not without synthetic complications. It has been demonstrated that bicyclobutane will be predominant if the geminal dibromocyclopropane is tetra-substituted at the remaining carbons. Otherwise allenic compounds will result, as has been shown by the work of Doering and La Flamme[88]. Nevertheless, as shown in equation 9, tetra-substitution does not guarantee that bicyclobutane will be the sole product[89].



(9)

An exception to the tetra-substitution requirement is exhibited by cyclopropyl systems which carry a *t*-Bu group geminate to the reactive C–H group (equation 10)[90]. In this

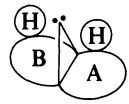


(10)

reaction the ratio of bicyclobutane/allene is 2/3. It was suggested that the steric compression exerted by the bulky *t*-Bu group sets up the methyl C–H bond in a position favoring C–H carbene insertion as shown in **24**.

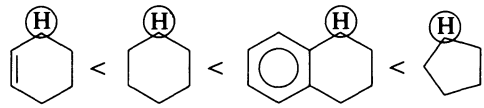
(24)

In system **25**, the carbene can insert into two different C–H bonds. Paquette and coworkers established in a series of similar systems the following order of preference for

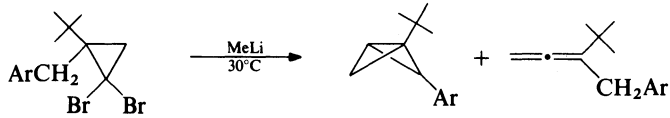


(25)

carbene insertion into the C–H bonds belonging to cycles A and B in **25**. This order was also ascribed to the proximity of the C–H bond to the carbenoid center[91].

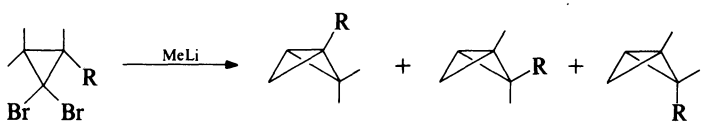


The selectivity of the insertion reaction as a function of the substituents on the aryl group was determined in the following reaction (equation 11). The ratio bicyclobutane/



(11)

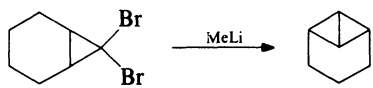
allene was found to exhibit a very small sensitivity to the substituents on the aryl group ($\rho = -0.5$)[92]. The low selectivity is also demonstrated in the following reaction (equation 12) in which all three possible isomers were observed[93, 94].



(12)

R = -CH=CH$_2$, *i*-PrCO

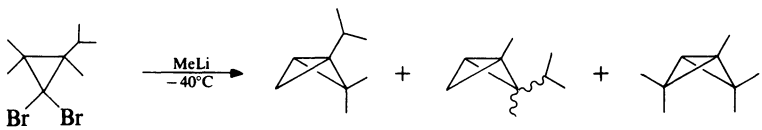
Another exception to the tetra-substitution requirement is provided by the reaction of **26** (equation 13)[95]. In this case, allene formation is prohibited for steric reasons.



(13)

(**26**) 37%

Although carbenes in general prefer to insert into C–H bonds in the order tertiary > secondary > primary[96], in the case of **27**, no insertion into the isopropyl group

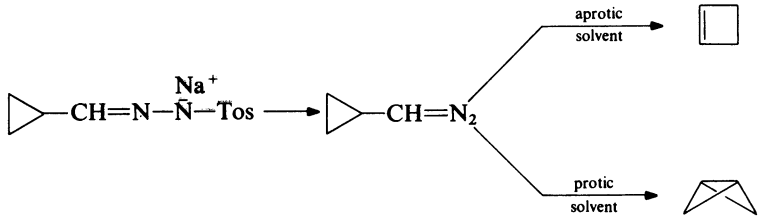


(14)

(**27**) not observed

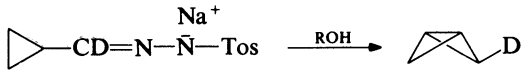
was observed. The product seems to derive exclusively from an insertion into the methyl C–H bond (equation 14)[97].

An additional method for the formation of bicyclobutane by a side bond formation involves the decomposition of cyclopropanecarboxaldehyde *p*-tosylhydrazone salts[98,99]. While in aprotic solvents this gives mainly ring expansion to cyclobutene, bicyclobutane is obtained in protic solvents, probably by a cationic mechanism[2,99–101] (equation 15).



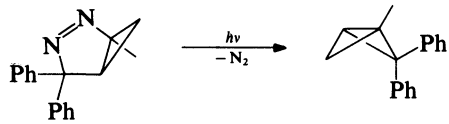
(15)

As was shown by Wiberg and Lavanish, the reaction is stereospecific[101] and a deuterium atom on the carbinyl group assumes an *exo* position in the product (equation 16). We close



(16)

this section with an example for a process in which the formation of the side bond can be envisioned as radical combination reaction (equation 17)[102,103].

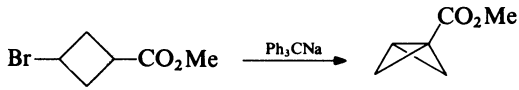


51%

(Ref. 102) (17)

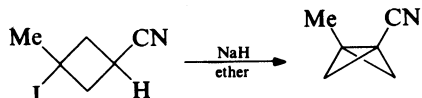
2. *Case B*

Bridging cyclobutane by a 1,3-elimination process was the first[1] and remains the most popular way to prepare bicyclobutanes. This can be achieved in several ways. Eliminations of HX have been reported for cases where X is either halogen[104–107], tosyl[106] or amine[108]. This requires activation of C(1) by an electron-withdrawing group such as CN or CO_2Me



(Ref. 1) (18)

(equation 18). Another example of this reaction is reported by Blanchard and Cairncross (equation 19)[104]. It should be pointed out that the presence of an activating group is not

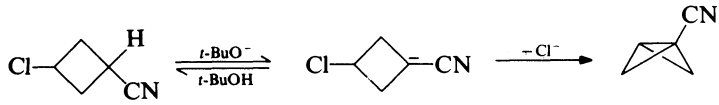


92.5%

(19)

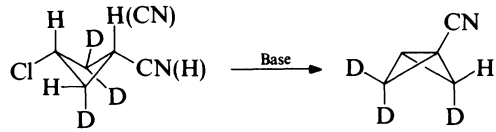
always sufficient to induce a 1,3-elimination reaction. Thus, using CN as an activating group and F as a leaving group, 1,2- rather than 1,3-elimination was observed[109].

The 1,3-elimination reaction was studied in depth by Hoz and coworkers[110] and found to be a stepwise process in which the proton is reversibly removed from the substrate (equation 20). The carbanion formed in this way has a very low barrier for inversion[111].



(20)

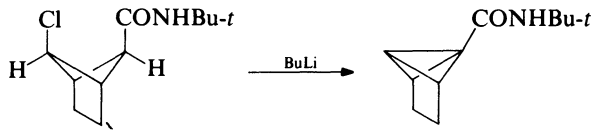
Nevertheless, the second step of this reaction seems to be stereospecific as was shown by Hall and coworkers[107]. They have prepared a mixture of the two isomers of **28** in which a hydrogen on one methylene bridge was *trans* to the Cl. In the product, the hydrogen visible in the NMR spectrum other than the bridgehead hydrogen was at the *exo* position (equation 21). This result indicates that the chloride is expelled from an equatorial position



(21)

(**28**)

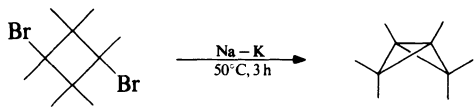
and is in accordance with a theoretical study regarding the reversal of this step[79]. It should be pointed out, however, that the nucleofuge can be expelled also from an axial position, as was demonstrated by Meinwald and coworkers[112] in the following reaction (equation 22).



(22)

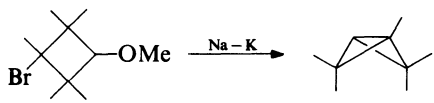
It is interesting to note that when the positions of the proton and the activating group are exchanged so that the proton assumes an axial position, no reaction was observed.

An alternative route to the formation of the carbanion and the 1,3-elimination process is via a Wurtz-type reaction[107, 113–115] (equation 23).



(Ref. 114) (23)

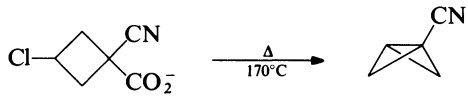
When the carbanion is stabilized by a cyano group for example, alkoxides are not expelled from the γ-position[111], and as was mentioned before, the reaction takes place only with good leaving groups such as halogens. However, in the absence of an electron-withdrawing group which is capable of stabilizing the negative charge, the highly reactive



(24)

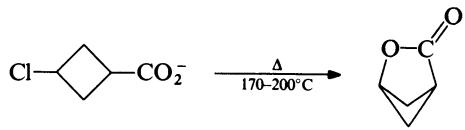
carbanion can displace even a sluggish leaving group such as methoxide[116–118] (equation 24).

Decarboxylation reactions provide another route to the formation of a carbanion, thereby initiating this way the γ-elimination reaction (equation 25). In the absence of an



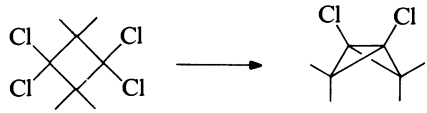
(Ref. 107) (25)

activating group on C(1), the pyrolysis of the carboxylic salt does not yield bicyclobutane. Instead, other reactions such as lactonization (equation 26) are observed[119].

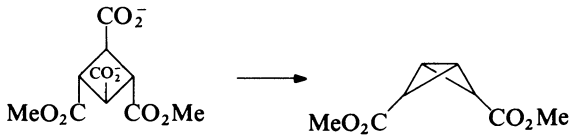


(26)

Electrolytic reactions (cathodic as well as anodic) were also employed in the synthesis of bicyclobutanes (equations 27 and 28 respectively).



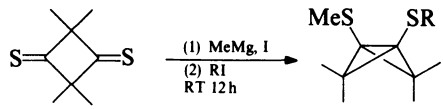
(Ref. 120) (27)



15%

(Refs 121, 122) (28)

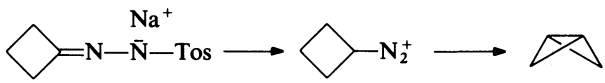
An interesting reaction by which the bridge bond is formed is shown below (equation 29).



(Ref. 123) (29)

R = Me, Et 79–100%

Pyrolysis of tosylhydrazone salts and other deamination reactions of cyclobutane derivatives yield bicyclobutane (equation 30)[124].

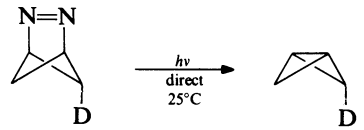


60%

(30)

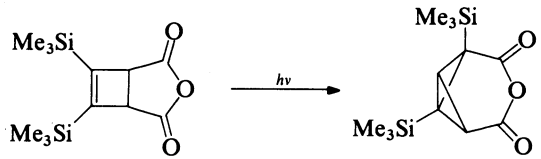
Photolysis, as well as thermolysis, of **29** also result in the formation of bicyclobutane[125]. Starting with **29** labeled with deuterium at the *exo* position gives upon photolysis a 47% excess of the double-inversion product (equation 31). However, this is in sharp contrast with the solution phase thermolysis of **29-d** which results in stereorandomization in the product[126].

(29)



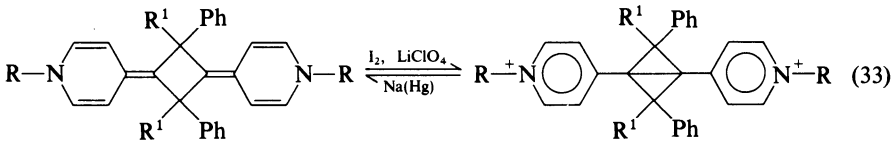
(29-d) 55% (31)

Compound **30** undergoes a photochemical transformation producing a bicyclobutane derivative (equation 32)[127]. This is a $\pi_{2a}+\sigma_{2a}$ reaction, in which the formation of the central bond is accompanied by the migration of the anhydride bridge.



(30) (32)

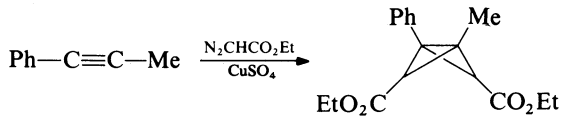
The last reaction to be mentioned in this section is the reversible oxidation of **31** (equation 33)[128].



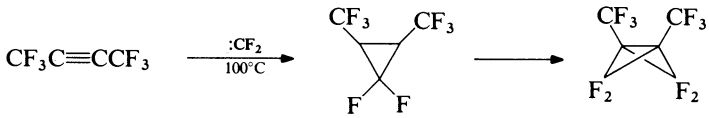
(31) (33)

3. Case C

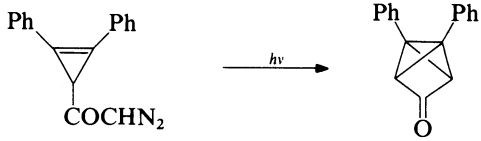
In this class of reactions the side methylene bridge is introduced to the molecule by bonding it to the two bridgehead carbons. Naturally, a reaction in which a carbenoid is inserted into a cyclopropene system is most commonly employed. In fact, in many cases, carbene is inserted first into an acetylenic derivative and then again into its product yielding finally the bicyclobutane framework (equations 34, 35). This method was successfully employed in the synthesis of highly strained derivatives of bicyclobutane (equations 36, 37).



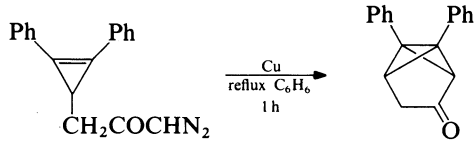
(Ref. 129) (34)



(Ref. 130) (35)



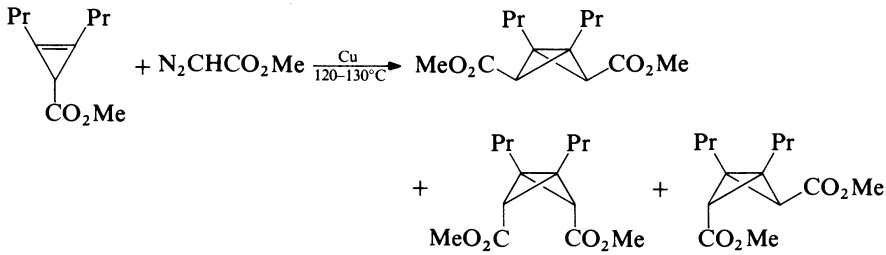
(Ref. 132) (36)



57%

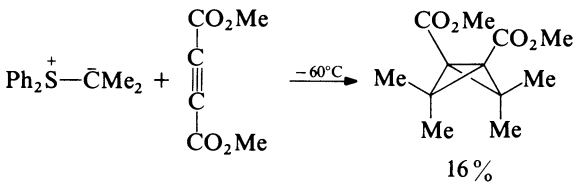
(Ref. 133) (37)

The insertion reactions are not stereospecific and in the following (equation 38)[134] and similar cases[61], all three isomers (*exo–exo*, *endo–endo*, *exo–endo*) were obtained.



(38)

A similar but probably non-carbenic reaction was reported by Corey (equation 39)[135]. This probably involves a repetitive nucleophilic attack followed by an internal nucleophilic displacement.

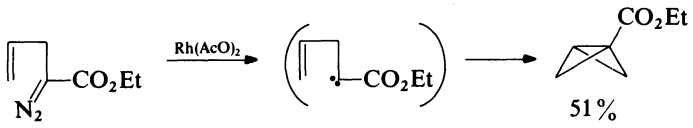


16%

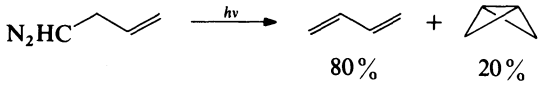
(39)

4. Case D

The simultaneous formation of a side and a central bond in bicyclobutane is always achieved by an intramolecular insertion of a carbene into a double bond as exemplified in the following reactions (equations 40, 41).

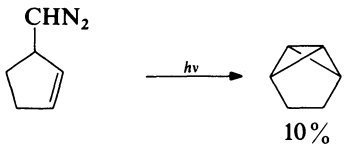


(Ref. 136) (40)

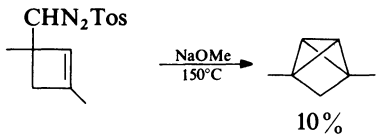


(Ref. 137) (41)

The method has also been employed for the formation of highly strained systems (equations 42, 43).

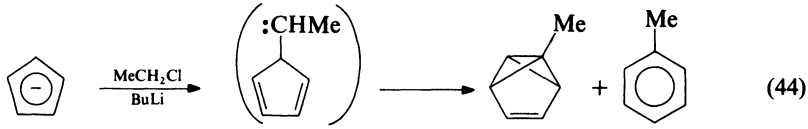


(Ref. 138) (42)



(Ref. 59) (43)

An interesting variant was observed by Christl and coworkers (equation 44)[31].



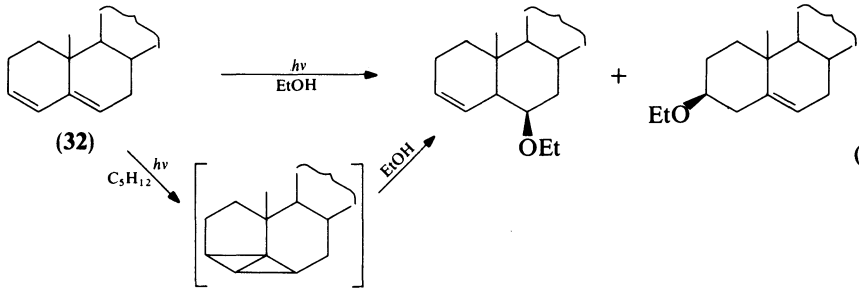
(44)

5. Case E

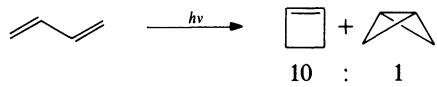
The majority of the reactions in which two opposite C–C side bonds are formed in one step are based on phototransformations of butadiene derivatives.

Irradiation of 3,5-cholestadiene (**32**) leads to the formation of a highly strained bicyclobutane incorporated in the molecular framework (equation 45). The product has never been isolated even from reactions carried out in a relatively inert solvent such as pentane. Its existence has been inferred from the products obtained in alcoholic media[139–141].

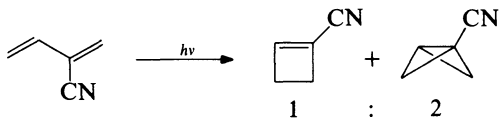
Butadiene itself also undergoes this reaction[142] yielding bicyclobutane and cyclobutene in a 1 : 10 ratio respectively (equation 46). A different proportion of the two cyclic systems are obtained in the reaction of 2-cyanobutadiene (equation 47)[143].



(45)

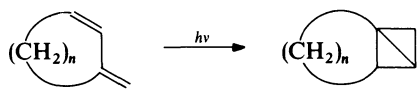


(46)



(47)

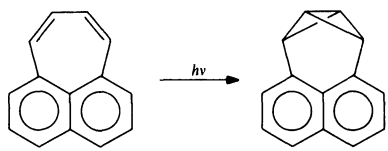
The rate by which bicyclobutane is photochemically generated depends on the strain in the product. Increasing the strain ($n = 3 > 4 > 5$, equation 48) reduces the production rate[144].



(48)

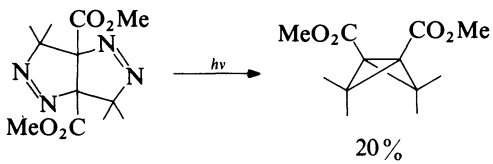
It was suggested[145] that bicyclobutane formation from conjugated dienes occurs in a concerted fashion from vibrationally relaxed singlet having an allyl anion–methyl cation electronic configuration.

A case where bicyclobutane was produced by irradiation of a *cis* diene is shown in the following example[146].



(49)

Another reaction which falls into this category and does not employ a conjugated diene was reported by Franck-Newman (equation 50)[147].



(50)

6. Case F

To the best of our knowledge there is no reported precedent for a reaction in which two vicinal C–C bonds each belonging to a different cyclopropyl ring are formed in a concerted fashion.

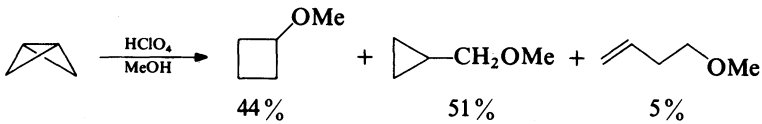
V. REACTIONS OF BICYCLOBUTANE

A. Electrophilic Additions

Two major aspects are involved in the additions of electrophiles to bicyclobutane, namely the product distribution and the stereochemistry of the reaction. In the following section we will address acid-catalyzed additions to bicyclobutane. This will be followed by a discussion of the addition of other electrophiles such as halogens, and will be concluded by a general discussion of the mechanism of electrophilic additions to bicyclobutanes.

1. Acid-catalyzed additions

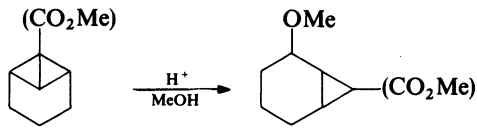
The reaction of bicyclobutanes with acids can result in the formation of three major products. Thus, when bicyclobutane itself is allowed to react with $HClO_4$ in MeOH (equation 51), cyclobutyl, cyclopropylcarbinyl and allylcarbinyl derivatives are obtained[148]. In most cases, the allylcarbinyl products are obtained only in minute amounts



(51)

and are sometimes completely absent from the reaction mixture. In the H_2SO_4-catalyzed hydration of bicyclobutane, for example, cyclobutanol (55%) and cyclopropylcarbinol (45%) account for 100% of the products obtained[65].

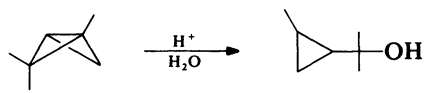
The proportions in which the two cyclic products are obtained seem to depend primarily on the substituents present and only to a lesser extent on the reaction conditions. Thus, acid-catalyzed addition of MeOH to **7** with or without a carbomethoxy group at the bridgehead position[76,149] results essentially in the sole formation of the norcarane



(52)

(7)

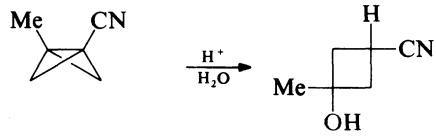
derivatives (equation 52). Similarly, the hydration of **33** in water results in a quantitative formation of **34** (equation 53)[87].



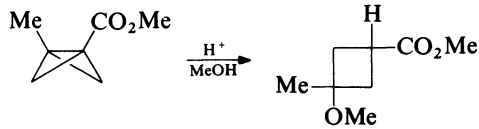
(53)

(33) **(34)**

Changing the medium drastically from water to pentane, does not significantly affect the reaction course, and the cyclopropane derivatives still account for ca. 94 % of the products in this reaction[86]. On the other hand, cyclobutyl derivatives are the sole products in the acid-catalyzed hydration of 3-methylbicyclobutanecarbonitrile (equation 54)[104] and in the methanolysis of methyl 3-methylbicyclobutanecarboxylate (equation 55)[65].



(54)



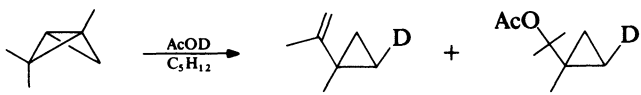
(55)

The partial data presented above seem to indicate that substituents which are capable of stabilizing a carbocationic center at a bridgehead position will favor the formation of cyclobutyl derivatives, whereas such a substitution on the methylene carbons results in cyclopropylcarbinyl derivative formation. This is consistent with the observation that the acid-catalyzed methanolysis of 3-*R*-bicyclobutanecarbonitrile (**35**) yields 58 % and 42 % of

(35)

cyclobutyl and cyclopropylcarbinyl derivatives respectively, for R = H, whereas for R = Me or Ph, only cyclobutyl products are obtained[150].

The acid-catalyzed additions to bicyclobutanes are highly stereospecific with respect to both the addition of the proton and the entrance of the nucleophile. In cases where cyclopropylcarbinyl products are obtained, protonation occurs with retention of configuration. As was shown by various groups, the proton incorporated always appears *cis* to the carbinyl moiety[86, 76, 149, 151]. This is demonstrated in the reaction of **33** with AcOD (equation 56)[86].



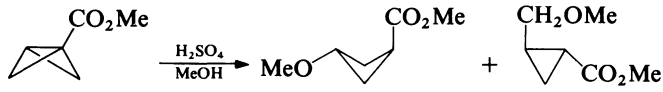
(56)

(33)

In most cases where cyclobutanes are formed, the only isomer obtained is one in which the proton and the nucleophile are positioned *cis* to each other[65, 104, 149, 151]. (An exception was observed for **35**, R = Ph. In this case, a 2 : 1 ratio of the two isomers was observed[150].) Thus, the high stereospecificity observed in the proton addition reactions is also typical of the step in which the nucleophile is incorporated into the product.

It is interesting to note that *cis* addition takes place even in cases where the

thermodynamic driving force operates in the opposite direction. In 1,3-disubstituted bicyclobutanes, the *cis* isomer is more stable than the *trans*, since in this configuration both bulky substituents can simultaneously adopt equatorial positions[152]. Yet, *cis* addition will place a bridgehead substituent *trans* to the entering nucleophile, resulting in the formation of the less stable isomer. This has been demonstrated in the acid-catalyzed addition of methanol to methylbicyclobutanecarboxylate (equation 57).

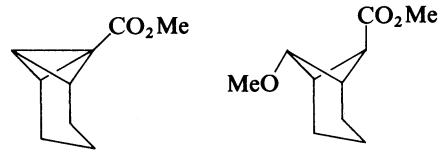


(Ref. 151) (57)

There are two possible modes for the observed *cis* addition, diaxial (**36**) and diequatorial (**37**).

(**36**) (**37**)

In order to establish the preferred direction of approach, the bicyclobutane moiety must be incorporated in a rigid system to prevent ring flips which equilibrate the axial and equatorial positions in the cyclobutanic products. The tricyclic system **7** is in principle an ideal substrate for this purpose. However, it reacts with acids to give mainly the corresponding cyclopropylcarbinyl derivatives. In the reaction of its carbomethoxy derivative **38** with $HClO_4$ in MeOH, Razin and Eremenko[149] have obtained 0.8% of the bicyclic product **39**, indicating that the addition mode is indeed *cis* diequatorial. This



(**38**) (**39**)

conclusion is clearly supported by data from the reactions of bicyclobutanes with other electrophiles such as halogens, $Hg(OAc)_2$ etc. (see Section V.A.2 below).

2. *Addition of halogens and mercuric salts*

Compared with the relatively large body of data available for the addition of acids to bicyclobutanes, there are only few reports on the reactions of other electrophiles. Among these, halogenation reactions comprise the major part of the data. Fewer results are available for other electrophiles such as $Hg(OAc)_2$, SO_2 or chlorosulfonyl isocyanate.

Unlike the reactions with acids, most of the reactions of halogens were performed in CCl_4. Although the mechanism in its intimate details may be different from that in protic media, the general features of the reaction are largely retained. Thus, the reactions are not completely stereospecific since some percentage of the second isomer could also be detected. For example, in the bromination of unsubstituted bicyclobutane, the *cis* dibromide accounts for 44% of the products whereas the *trans* isomer is obtained in 19% yield (equation 58)[65].

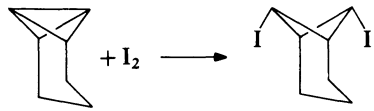
(58)

Iodination reactions seem to yield in most cases only the *cis* isomer[86, 153]. In cases where the *trans* isomer was also obtained[65, 86], it was suggested that it was formed by an isomerization reaction.

Due to their larger size compared with protons, it could have been assumed that halogens could form a bridged bicyclobutonium structure (**40**) and therefore will approach

(**40**)

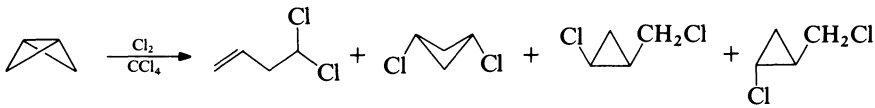
the molecule from an axial direction. However, nucleophilic attack on this bridged structure at the second step will probably lead to the formation of the *trans* isomers of the adducts. Yet, in most cases, the *cis* isomer was the main product. Iodination of **7** is another example of the formation of a *cis* addition compound, **41**, in which X-ray analysis showed that the two iodine atoms assume equatorial positions[154] (equation 59). Stereospecificity



(59)

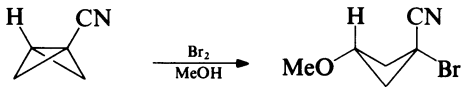
(**7**) (**41**)

was also observed in chlorination reactions. In the reaction of bicyclobutane with Cl_2 in CCl_4 (equation 60), 41 % of the cyclopropyl derivative are in the *cis* configuration whereas only 6 % of the *trans* isomer is obtained[76].



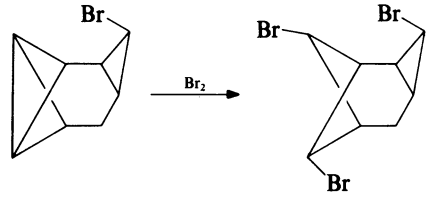
45 % 4 % 41 % 6 % (60)

From the products distributions obtained in the various halogenation reactions, it seems that there is a correlation between the electronegativity of the halogen employed and the distribution of the products. The more electronegative the halogen is, larger amounts of rearranged products are obtained. With halogens of lower electronegativity, i.e. I_2, mainly cyclobutane derivatives are obtained. However, this conclusion must await further experimental verification. It seems also that in halogenation reactions the cyclobutane structure is retained in the products more than in acid-catalyzed reactions. Thus for example, acid-catalyzed addition of methanol to bicyclobutanecarbonitrile (**35**, R = H) results in the formation of ca. 40 % of the cyclopropyl derivative[150], whereas the sole product of the reaction of this substrate with Br_2 is **42** in which the cyclobutane ring is retained (equation 61)[155].



(35, R = H) (42) (61)

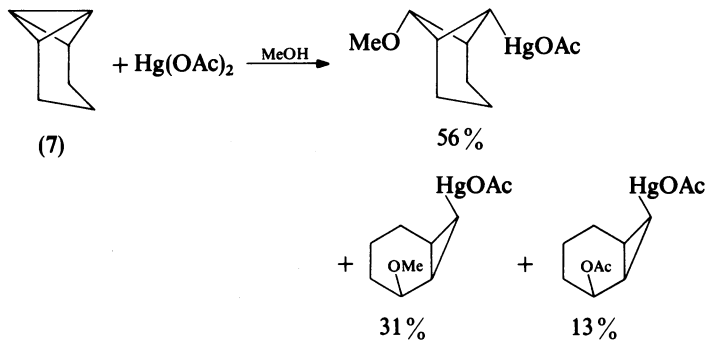
An interesting case of inverted stereospecificity was observed by Christl and Lang[156]. In this case, Br_2 adds across the central bond of the bicyclobutane moiety *trans* rather than *cis* (equation 62). Although the possibility of a radical reaction was entertained in this case, it is



(62)

highly likely that this is also an electrophilic reaction, and that the inversion in the stereochemistry can be attributed to the steric hindrance exerted by the bromine atom on the cyclopropyl ring.

Even fewer data are available for the reactions of mercuric salts with bicyclobutanes. The general pattern of giving both cyclopropyl and cyclobutyl products is observed in these reactions as well[157–159]. Thus for example in the reaction of $Hg(OAc)_2$ with 7 the products are norcaranyl and norpinyl derivatives (equation 63)[157].

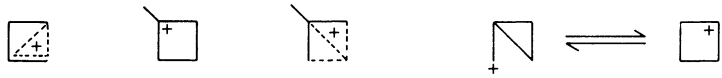


(7) (63)

3. Mechanism

As was pointed out earlier, either central bond cleavage or addition to a side bond can account for the formation of the various products obtained in electrophilic addition reactions. It is highly likely that, in reactions where the cyclobutane ring is retained in the product, it is the central bond which is cleaved. However, when cyclopropylcarbinyl derivatives are obtained, both attack on a side bond as well as cleavage of the central bond followed by skeletal rearrangements are conceivable mechanistic pathways. The literature does record one report which purportedly disproves the side bond fission process in the reaction of chlorosulfonyl isocyanate with bicyclobutane[160]. The results of this study, however, have been reinterpreted[161], leaving the question moot.

The nature of the cation formed in the first step is highly controversial. On the basis of solvolytic studies, in which cyclopropyl as well as cyclobutyl derivatives are obtained, Roberts and coworkers suggested[162] that the bicyclobutonium ion is in fact non-classical with a delocalized σ structure (**43**). On the basis of NMR studies, classical as well as non-classical structures (**44**, **45** and **46**) were suggested for this species and its derivatives.



(43) **(44)** **(45)** **(46)**

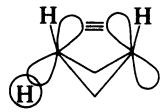
(Ref. 162) (Ref. 163) (Ref. 164) (Ref. 165)

However, a detailed discussion of the cyclobutyl–cyclopropylcarbinyl rearrangement is beyond the scope of this chapter and the following discussion will therefore be confined to the formation of cyclobutane derivatives only.

In the absence of skeletal rearrangements, the reaction consists of two main steps: (*a*) an electrophilic addition leading to a carbocationic intermediate; and (*b*) a subsequent nucleophilic attack on this cation.

A late transition state is expected for the first step of the reaction, since it leads to the formation of an unstable species. An experimental manifestation of this was observed by Hoz and Livneh[150] in the acid-catalyzed addition of MeOH to **35**. The reaction was found to be general acid-catalyzed with a Bronsted α value of 0.98. In the second step of the reaction, the cyclobutyl cation is trapped by a nucleophile which usually enters the molecule *cis* to the proton or to any other attacking electrophile. Since this phenomenon was observed with a variety of substituents at the bridgehead position as well as with a spectrum of electrophiles, a 1,3 steric hindrance to the approaching nucleophiles is not likely. An alternative explanation of this phenomenon is that the cyclobutyl cation is obtained in a bent structure with the equatorial side more exposed to nucleophilic attack.

Several theoretical calculations seem to confirm the latter hypothesis. Extended Huckel calculations reported by Baldwin and Foglesong[166], refute the previous results of Davis and Ohno[167] and show that the cation is indeed highly puckered. Furthermore, they find that the hydrogen on the charged carbon adopts an axial conformation and that there is a significant degree of bonding across the ring. CNDO calculations by Trindle and Sinanoglu[168a] and Wiberg and coworkers[168b] have further confirmed Baldwin's results. These calculations have shown that a considerable amount of positive charge is transferred to the equatorial hydrogen on C(1)(+0.147 as compared to +0.095 for the axial hydrogen). This was interpreted by Wiberg[168b] to mean that there is an appreciable overlap between the empty orbital on C(3) and the p component of the equatorial hydrogen on C(1) as shown in **47**. Nearly a decade later, Hehre and coworkers[169]



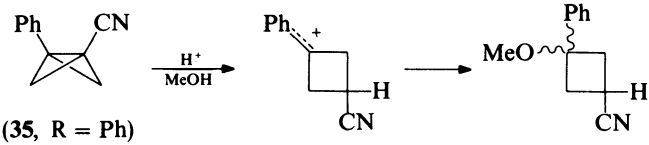
(47)

recalculated the bicyclobutonium ion at the 4-31G level and found that the ring is indeed highly puckered with H(1) deviating from the neighboring three-carbon plane toward the

axial position by ca. 36°. However, they also found that this geometry corresponds to an energy maximum on the potential energy surface and can 'glide' in a barrierless motion to the cyclopropylcarbinyl structure. Thus, the puckered cyclobutyl cation is a transition state rather than a stable entity. In a recent paper Dewar and Reynolds[170] refuted this conclusion showing by MINDO/3 that the puckered cyclobutyl cation does present a minimum on the $C_4H_7^+$ potential surface. Moreover, this cation was found to be even more stable than the cyclopropylcarbinyl cation by 5.6 kcal mol^{-1}. Somewhat earlier Jonvik and Boggs had reported[171] that *ab initio* calculations (4-21G basis with enforced C_s symmetry) predict the cyclobutyl cation to be only slightly puckered with H(1) lying 4.8° towards the axial position. A slightly puckered cation was also suggested by Bauld and coworkers[48] (MINDO/3).

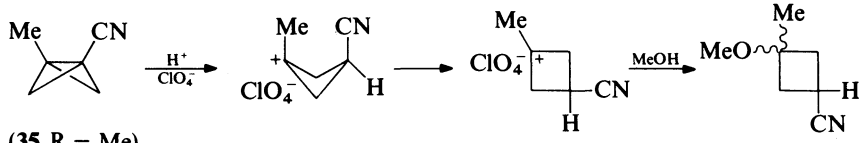
The analysis of the results gathered from the various reports suggests the possible existence of two cations which differ in the degree of puckering. Using a 3-21G basis set, with the restriction of a C symmetry, Hoz and Cohen found[172] that indeed there are two energy minima for the cyclobutyl cation. Both structures are puckered and differ from each other in the degree of flatness. The more puckered structure is lower in energy by ca. 3.0 kcal mol^{-1}.

Thus, if a nucleophilic attack occurs on the more stable puckered cation, it will result in an overall *cis* addition. In cases where the charge on C(3) can be effectively stabilized by a substituent at this position, the ring will open to a nearly planar conformation which will allow the nucleophile to approach from both sides. This was indeed observed[150] in the reaction of **35**, R = Ph, where both isomers were obtained (equation 64).



(**35**, R = Ph) (64)

The *trans* isomer can also be obtained if the reaction is performed in the presence of a non-nucleophilic anion. In the presence of 0.6 M $NaClO_4$, the reaction of **35**(R = Me) with tosylic acid in MeOH results in the formation of 25% of the *trans* isomer as opposed to <2% in the absence of this salt[150]. This can be interpreted as a trapping of the puckered cation by the ClO_4^- from an equatorial direction, allowing it to open to the planar form before it is trapped by a MeOH molecule (equation 65).

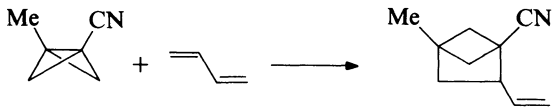


(**35**, R = Me) (65)

B. Reactions with Double Bonds

The Diels–Alder reaction is probably the only reaction which is known to occur with olefins and not with bicyclobutanes. Thus when **35**(R = Me) was allowed to react with butadiene, no typical Diels–Alder adduct was obtained[173]. Instead, the cycloadduct **48** was observed (equation 66).

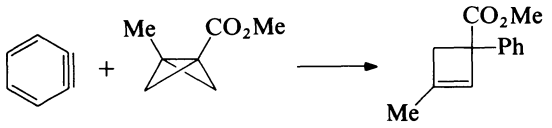
This interesting result is not unexpected since, as was pointed out in Section II.B, the constituents of the bonding orbital of the central bond are not properly oriented for efficient overlap with the corresponding orbitals on the diene moiety.



(66)

35(R = Me) (**48**)

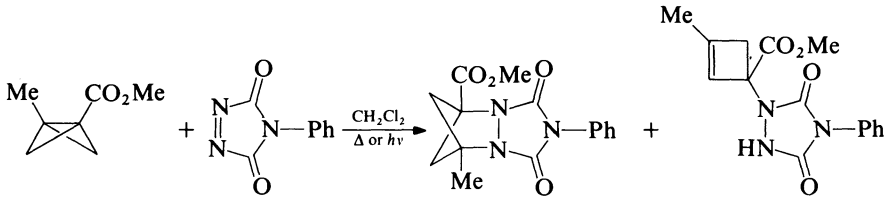
Another reaction which is commonly observed is the 'ene' reaction. This is exemplified by the reaction of benzyne with **49** (equation 67)[105]. It was suggested[174] that the double



(67)

(**49**)

bonds can be classified into two groups according to their reactivity and the type of product which is obtained in their reaction with bicyclobutane. Strongly electron-deficient double bonds such as hexafluoroacetone[120] and 1,1-dicyano-2,2-bistrifluoromethyl-ethylene[104] react very rapidly at room temperature and give mainly the 'ene' products. On the other hand, the reactions of the less reactive double bonds, e.g. acrylonitrile and various styrenes, with bicyclobutane are usually conducted at elevated temperatures (100–150°C)[173]. These reagents lead mainly to the formation of cycloadducts. However, there are several exceptions to this rule. A recent example is the reaction of triazolinediones with **49** (equation 68)[175].



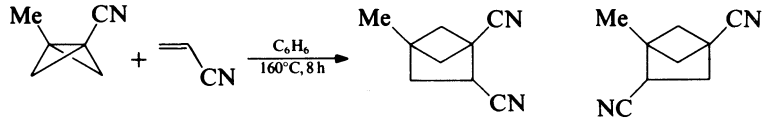
(**49**)

(68)

Two mechanistic aspects are of interest with respect to these reactions: (1) the mode of the reaction, namely, whether the reaction is radical, ionic or concerted, and (2) the stereochemical course of the reaction, i.e. the direction of approach of the double bond.

The possibility of a concerted [2 + 2]cycloaddition reaction in this case is unlikely since these thermal reactions are known to be symmetry forbidden[176].

It has been demonstrated that the addition of olefins and acetylenes to bicyclo[2.1.0]pentane occurs via the formation of a diradical intermediate[177, 178]. Literature data support this conclusion for the reactions of bicyclobutane as well. Thus, in the reaction of **35**(R = Me) with acrylonitrile[173], there are two possible cycloadducts, **50** and **51** (equation 69). An ionic reaction in which the olefin serves as an electrophile should lead to an intermediate in which the positive charge is located α to the methyl rather than to the cyano group of the cyclobutyl moiety. Ring-closure in the following step will result in the formation of **51**. Yet this product was not observed and the reaction yielded only the second isomer, **50**, thus supporting a radical course for the reaction.



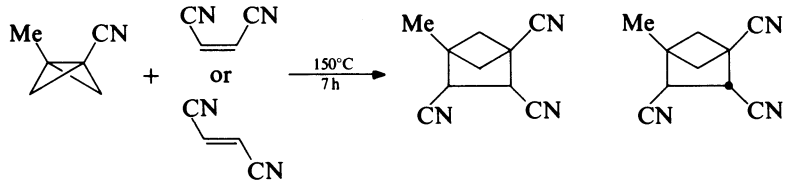
(69)

41%

(50) (51)

not observed

Also consistent with a radical reaction is the partial loss of stereochemistry observed in the reaction of maleonitrile and fumaronitrile with the same substrate (equation 70)[173].

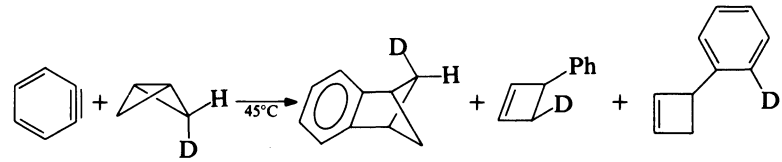


(70)

It should be pointed out, however, that in other cases an electrophilic reaction cannot be totally excluded. By virtue of the substituent effect, such a mechanism was invoked for the reactions of the highly electrophilic triazolinedione with bicyclobutane derivatives (equation 68)[175].

In contrast with the cycloaddition reactions, no definite conclusion is available for the 'ene reaction'. These reactions can be rationalized as proceeding via either a one- or a two-step reaction[174].

The reaction of benzyne with bicyclobutane was employed in two different laboratories to show that the double bond approaches the substrate from its rear side. Pomerantz and coworkers[174, 179, 180] reacted benzyne with bicyclobutane labeled with deuterium at an *endo* position. Cycloaddition as well as 'ene' reaction products were obtained (equation 71).

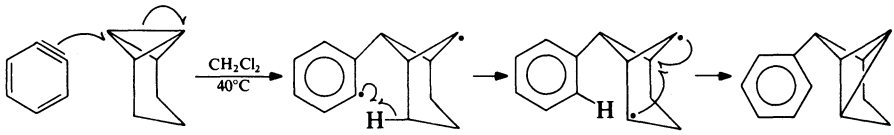


(71)

(52) (53) (54)

In the cycloadduct **52** the deuterium atom was found at the *endo* position, indicating that the double bond indeed approaches the bicyclobutane molecule from its rear end. In the 'ene' reaction product, the deuterium appeared in two positions. When found on the cyclobutene ring **53**, it is located *cis* to the phenyl ring; otherwise (**54**), it is found at the *ortho* position of the phenyl ring. Both products are consistent with a rear side attack.

A different approach was utilized by Gassman and Richmond[181, 182]. In order to prevent the flip process which equilibrates axial and equatorial positions in the cyclobutane product, benzyne was allowed to react with **7**. The phenyl group assumes an *endo* position in the product, thereby confirming the assumption that the double bond attack takes place along an equatorial path (equation 72). It should be pointed out that the



61%

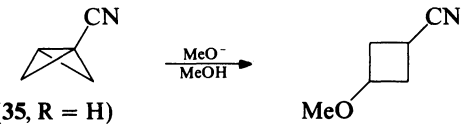
(72)

normal 'ene' reaction is not observed since the product of such a reaction would be in violation of Bredt's rule[183].

In conclusion, the reactions of double bonds with bicyclobutane are similar to electrophilic reactions with regard to the direction of approach. In most cases cycloadditions are radical reactions, whereas the formation of the 'ene' products is consistent with both radical and concerted processes.

C. Reactions with Nucleophiles

In a manner similar to that of olefins, bicyclobutanes substituted by electron-withdrawing groups at the bridgehead position can undergo facile nucleophilic attacks. Studies of alkoxide-catalyzed additions of alcohols to bicyclobutanecarbonitrile (**35**, R = H) (equation 73) using crotononitrile as a reference olefin (equation 74), showed that the two substrates resemble one another very much in both their reactivity and activation parameters[184].



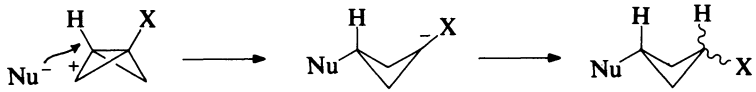
(**35**, R = H) (73)

$$MeCH{=}CHCN \xrightarrow[MeOH]{MeO^-} MeCH(OMe)CH_2CN \qquad (74)$$

Compared to cyclopropanes, bicyclobutanes certainly display a higher susceptibility to nucleophiles. The cleavage of a cyclopropyl ring usually necessitates the presence of two activating groups[185] whereas a single group at the bridgehead position is sufficient to promote nucleophilic cleavage of the central bond in bicyclobutane.

For nucleophilic attack by MeO^- in MeOH on bicyclobutane, the following order of activation by bridgehead substituents was found: COPh > CN = COOMe > SO_2Tol[186]. This resembles partially the order found for the same reaction in olefinic systems: COR > SO_2R > CN > COOR[187].

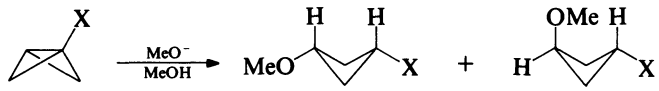
In general the reactions are believed to proceed in two steps. The first is a nucleophilic attack at position 3, followed by protonation of the carbanion formed α to the activating group X (equation 75).



(75)

The stereospecificity of the reactions is usually low. A single probable exception to this is the reaction of 3-methylbicyclobutanecarbonitrile with ammonia. In this case a single

isomer was isolated which was tentatively assigned a structure resulting from a *cis* addition reaction. In most cases, however, a mixture of two isomers is obtained. For example, in the reaction of bicyclobutanecarbonitrile and its carbomethoxy derivative with methoxide, two isomers are obtained in a ratio of 1 : 2 (equation 76)[107, 131]. This, however, could result

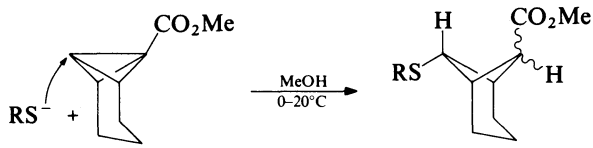


(76)

X = CN, CO_2Me 2 : 1

from a post-isomerization occurring under the basic conditions of the reaction. It is generally assumed that the more stable isomer is the one with the two bulky groups *cis* (diequatorial) to one another[152]. It was shown that under kinetically controlled conditions, the less stable isomer is preferentially obtained (e.g., in a ratio of 3.6:1 for **35**, R = H)[111].

Since the nucleophilic addition reactions consist of two distinct stages, the stereochemistry of each stage has to be considered. On the basis of the scarce amount of data available, it seems that nucleophiles, like electrophiles, approach bicyclobutane from an equatorial direction. This is an expected path since, viewed as an S_N2 reaction, the nucleophile approaches the substrate *anti* to the leaving group (the central bond). This has been experimentally demonstrated by the reaction of thiolate anions with **38**. In these reactions, RS was found to assume only an *endo* position (equation 77)[188]. This was also

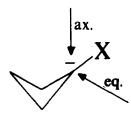


(77)

(38)

confirmed by *ab initio* calculations. Using a split level basis set it was found that the equatorial approach of H^- to bicyclobutane is largely preferred over the axial one[79].

In the absence of a post-isomerization reaction the product stereodistribution is determined at the protonation stage. Protonation of the carbanion could be either axial or equatorial (**55**).



(55)

In most cases *cis* addition slightly prevails. The striking preference for the formation of the less stable isomer by protonation was first noted by Zimmerman[189] for cyclohexane nitronates and enolates. This was assumed to result from an approach of the proton donor from the less hindered equatorial side. The same argument was applied also to the cyclobutyl anion[110, 111] although in this case there is only one hydrogen that can hamper the approach from the axial direction.

When the cyclobutyl moiety is not confined in a rigid ring system, ring flipping permits

protonation to occur on the two geometrical isomers **56** and **57** (equations 78 and 79). Equatorial protonation of **56** will lead to a transition state lower in energy than that of **57**

(78)

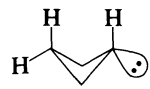
(56)

(79)

(57)

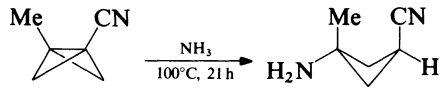
since an unfavored 1,3-diaxial interaction between the bulky groups X and Nu is built in the latter transition state.

Ab initio calculations on the reaction of H^- and bicyclobutane show[172] that in the course of the reaction, the hydrogen on the bridgehead position where the negative charge is developed moves toward an axial position. If the negatively charged carbon assumes a pyramidal geometry, the anion formed first will probably have the following geometry.



However, in order for this to be the origin of the *syn* addition, the protonation must effectively compete with inversion at the carbanionic center. In the absence of sufficient data an unambiguous conclusion cannot be drawn[190].

In addition to alkoxides, other nucleophiles whose reactions with bicyclobutane have been investigated are amines[104, 191] and thiolates[188]. In the reaction of **35**(R = Me) with ammonia, only one isomer which was assumed to be the product of a *cis* addition reaction was obtained (equation 80)[104]. However, with amines such as dimethylamine, diethylamine and piperidine, a mixture of isomers was obtained with *cis* addition products

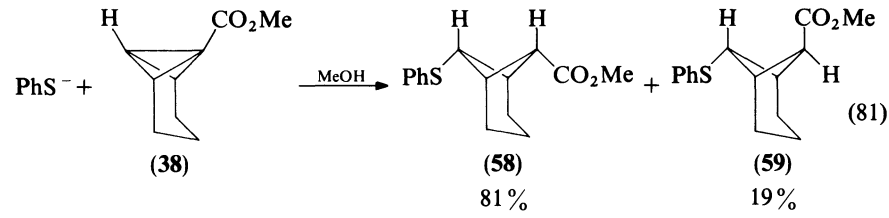


(80)

(35, R = Me)

prevailing[191]. It was found that the stereodistribution of the products is affected by the solvent. The percentages of the *cis* addition products were 77% in benzene, 80% in dioxane and in methanol only 64%. This observation led the authors to suggest an internal proton transfer from the ammonium ion to the carbanionic center as a possible origin for the overall *cis* addition.

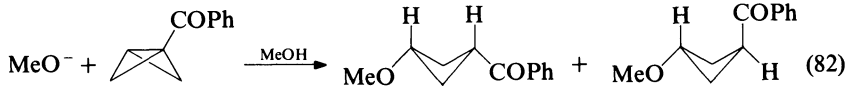
There seem to be two exceptions to the preference of the *cis* addition mode. The first is the addition of thiolates to **38** where the *endo–endo* product **58** (*trans* addition) was obtained in four-fold excess over the *endo–exo* isomer **59** (equation 81). It should be noted that such a preference was also obtained in the reaction of the same substrate with PhSH under free radical conditions[192]. Thus, it is reasonable to assume that in both cases, steric



(81)

(38) (58) 81% (59) 19%

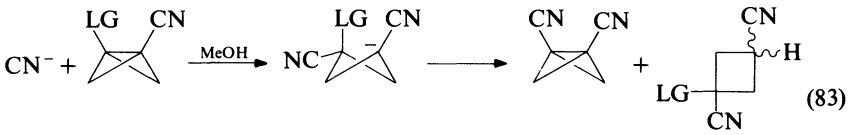
constraints of this specific system channel the reaction to the *trans* addition mode. Another example is given in equation 82[186].



(82)

2 : 1

A reaction which is typical of olefinic compounds is nucleophilic vinylic substitution. The most common mechanism of this reaction is addition–elimination[193]. A similar mechanism was also observed in the bicyclobutane system (equation 83)[190]. However,



(83)

LG = Cl	17%	40%
LG = Br	60%	0%

whereas in the olefinic systems the elimination step practically always competes effectively with protonation of the intermediate carbanion, in bicyclobutanes, this mechanism dominates only when the nucleofuge (LG) is a very good one, e.g. Br. When a somewhat more sluggish nucleofuge such as Cl is employed, protonation of the carbanion becomes the predominant reaction leading to an overall large proportion of addition reaction. The difference between the two evolves probably from the strain which builds up in the transition state of the elimination step.

D. Radical Reactions

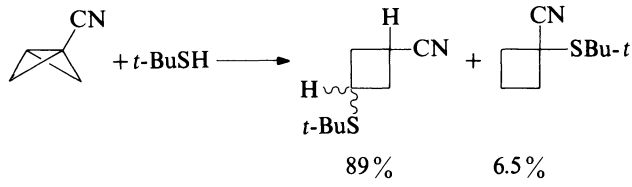
The reactions of bicyclobutane with radicals have been the subject of a relatively limited number of investigations. Two types of reactions have been observed: (1) addition to the central bond and (2) hydrogen abstraction. Which of the two reactions will occur is determined by the nature of the attacking radical. Thus, reagents such as thiyl radicals add across the central bond. On the other hand, *t*-butoxyl, which is generally the radical of preference for hydrogen abstraction, reacts with bicyclobutane to give the 2-bicyclobutyl radical.

1. Addition to the central bond

Most studies of radical addition to the central bond were performed with PhS, generated either thermally or photochemically from precursors such as PhSH or PhSSPh.

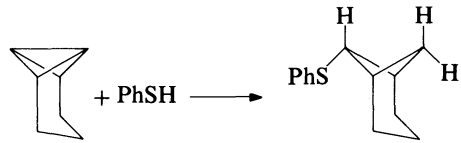
Reactions with other radicals, namely, photochemically generated α-keto radicals[194] and alkyl thiyl radicals[104, 107], exhibit results similar to those of PhS.

In most cases the addition is anti-Markovnikov. An exception is the reaction of **35**, R = H with *t*-BuSH[107] in which 6.5% of the other isomer was also obtained (equation 84).



(84)

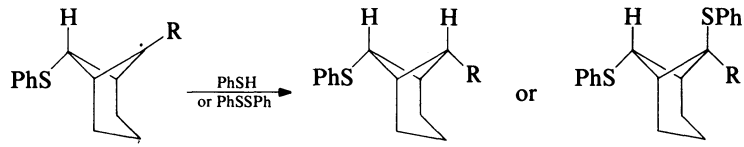
The data available indicate that the radical approaches the substrate along the equatorial direction. In the addition of PhS to tricyclo[4.1.0.0^{2,7}]heptane (**7**) (equation 85) it was demonstrated that equatorial attack is preferred over axial attack by a factor of at least 27 000[195, 196].



(85)

(**7**)

The stereochemistry of the second step is of special interest. Studies by Szeimies and coworkers have shown that in the system **60**, both H and PhS are trapped by the cyclobutyl radical preferentially from the axial direction[192, 195] (equation 86). The ratios of axial vs. equatorial attack are 1.5:6.



(86)

(**60**) main product

R = Ph, Me, Et, Bu

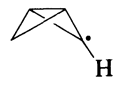
It should be pointed out that in nucleophilic reactions, where the second step is protonation, as well as in the capture of the carbocation formed in the course of electrophilic reactions with bicyclobutane, the reactive intermediates are preferentially trapped from an equatorial direction. *A priori*, there is no obvious stereoelectronic driving force for this exceptional behavior of the reaction of PhSH with **60**. However, in this specific case, it could stem from a steric repulsion between the methylene group at position 4 of the tricyclic system and the phenyl group of the PhS either entering or already present. Supporting this assumption are reactions of thiyl radical with bicyclobutane (equation 85)[104,107]. In the absence of the steric effects of the tricyclic system, the *cis* and *trans* isomers were obtained in equal amounts. Hence, at this stage, it seems that unlike the reactions of cyclobutyl carbanion or carbocation, stereoselectivity in the trapping radical

has not been demonstrated. Although in the reaction of 1,2,2-trimethylbicyclobutane with PhS, two isomers with a ratio of 4 : 1 were obtained, no structural assignment was made[197].

The relative rates of the reaction of PhS with tricyclo[4.1.0.0^{2,7}]heptanes were found to depend on the substituents at the bridgehead position. A linear correlation was observed between the relative rates and the vertical ionization potentials of the substrate[197].

2. *Hydrogen abstraction*

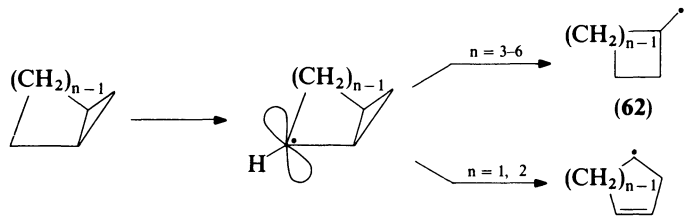
Hydrogen abstraction reactions seem to be the only reactions in which neither the central bond nor a bridgehead carbon is directly involved. The reaction takes place on one of the side methylene groups, leading to the formation of bicyclobut-2-yl radical (**61**). This radical was observed directly by ESR[198, 199].



(61)

An interesting point is the long range coupling constants (7.85 and 0.81 G) determined for the methylene protons. INDO calculations have indicated that the larger coupling constant is associated with H_{endo}[198]. This result has rendered the bicyclobutyl radical to be one of the few significant counter-examples to the empirical W-plane arrangement rule. The rule predicts that the larger coupling constant occurs where there is an approximate coplanar zig-zag arrangement of bonds between the p orbital containing the spin and the proton of interest[200]. However, a more recent *ab initio* study[201] has refuted the original INDO based conclusion, showing that when the p orbital containing the unpaired spin adopts an axial position (W-arrangement), the larger coupling constant is associated with H_{exo} rather than with H_{endo} as was originally claimed.

The abstraction of hydrogen from C(2) is typical of the general series of bicyclo[n.1.0]alkanes. Thus, the main reaction of these hydrocarbons with *t*-butoxy radicals is hydrogen abstraction from a position α to the cyclopropyl ring. This reaction is followed by a β-scission in which one of the cyclopropyl bonds is cleaved. Usually, the bond which is cleaved is the one which can assume an eclipsed conformation with the singly occupied orbital (SOMO). Hence, in the bicyclo[n.1.0]alkanes series, for n > 2, an outer bond is cleaved to give cycloalkenylmethyl radicals. However, for cases where n = 1 or 2, fission of the inner bond takes place yielding the cycloalkenyl radical (equation 87)[199].



(62)

(63)

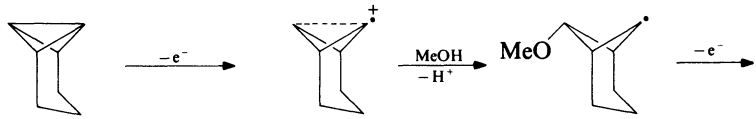
(87)

The latter occurs despite the fact that the central bond is orthogonal to the SOMO. The reason for this exceptional behavior has been attributed to a much greater strain relief in this process compared to that in which an outer cyclopropane bond is cleaved. Using the ring strain energies of the hydrocarbons as an approximation for those of the

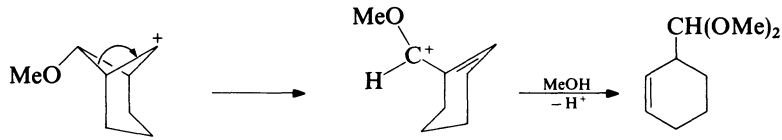
corresponding radicals, it can be seen that the formation of **63** (n = 1,2) is favored thermodynamically by ca. 25 kcal mol^{-1} over that of **62** (n = 1,2). For bicyclo[n.1.0]alkanes with n = 3–6, the differences in strain energies amount to less than 3 kcal mol^{-1} [199].

3. The radical cation of bicyclobutane

Electrochemical oxidation constitutes one of the two methods used to produce the radical cation of bicyclobutane derivatives. The radical cation obtained in this way undergoes nucleophilic addition of MeOH followed by a second oxidation step leading finally to **64** (equation 88)[202, 203].

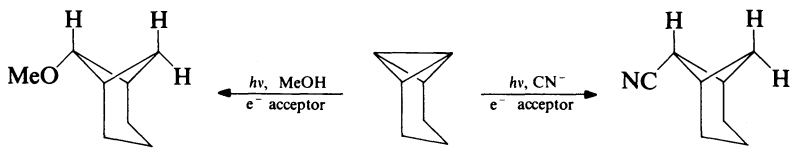


(88)



(64)

The radical cation can also be obtained by interaction of bicyclobutane with a photoexcited electron acceptor to which it transfers an electron[204, 205]. Examples of electron acceptors used are 1-cyanonapthalene and 9,10-dicyanoanthracene. The radical cations obtained in this way undergo various dimerization reactions (the course of which depends on the bridgehead substituents[205]) and in the presence of nucleophiles such as MeOH or CN^- undergo nucleophilic addition reaction (equation 89).

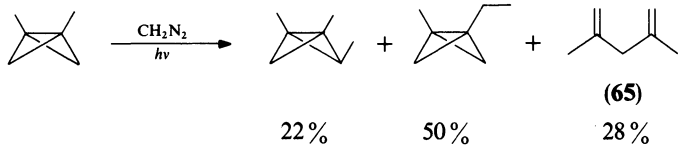


(89)

A detailed study by Roth and Schilling of the photochemically generated radical cation of **7** showed that different radical cations are obtained in CD_3CN and in $(CD_3)_2CO$[206]. These divergent results suggest the involvement of two different high energy occupied MOs on the substrate which are relatively close in energy[206].

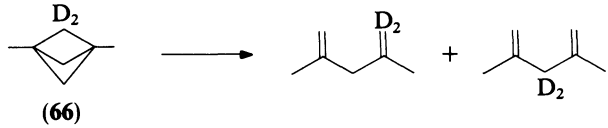
E. Reactions with Carbenes

Since in many cases the syntheses of bicyclobutane involve the intermediacy of carbenoids, it is only reasonable to assume that bicyclobutane is not highly reactive toward carbenes, at least when compared with its starting materials. The reactions usually yield a mixture of products (equation 90)[153]. Interestingly, a product of a bicyclopentane



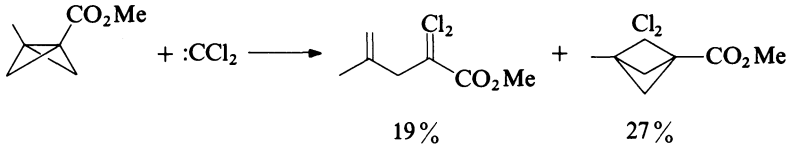
(90)

structure was not obtained in this reaction. The possibility that such a product is a precursor of **65** was ruled out by using carbene labeled with deuterium[153]. In this experiment, deuterium atoms appeared only in vinylic positions, whereas intermediacy of **66** must, due to its symmetry, yield deuteration on the central methylene carbon as well (equation 91). The high activation energy of the isomerization of bicyclopentane (49.6 kcal mol^{-1})[207], also argues against its intermediacy in this reaction.



(91)

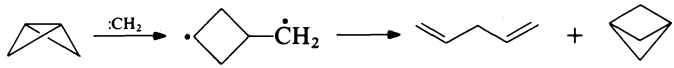
In the reaction of unsubstituted bicyclobutane with methylene, Wiberg and coworkers isolated 1% of bicyclopentane[65]. Larger yields were reported by Applequist and Wheeler[208] using dichlorocarbene in the following reaction (equation 92). However, this



(92)

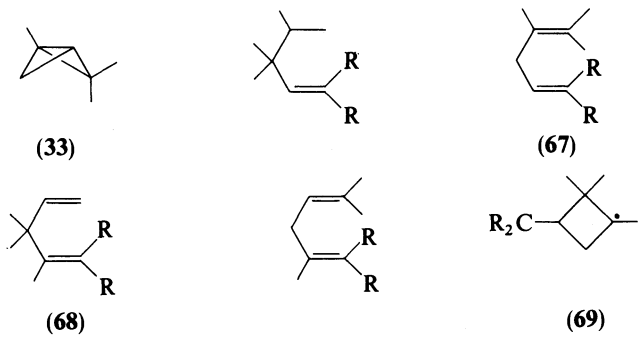
carbene was found to be inert toward other substrates such as 1,3-dicyano or 1,3-dimethoxycarbonyl bicyclobutane[208].

Two mechanisms were advanced for the reaction of carbenes with bicyclobutane. The first one is a stepwise addition (equation 93)[65]. This mechanism was challenged by Mock

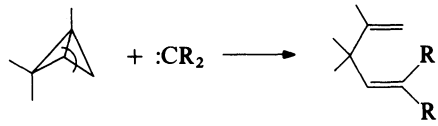


(93)

and Jones[209] on the following grounds. The reaction of :CR_2 with **33** can give in principle four different isomers of the dienic product. The optimal path will lead to the formation of



67 via **69**. Yet, in the reactions of **33** with $:CR_2$ where R = COOMe (obtained from irradiation of $N_2C(COOMe)_2$) or Cl (obtained from the reaction of t-$BuO^- + CHCl_3$), the only product isolated had the structure of **68**. Therefore, an alternative two bond 'pluck' one-step mechanism was suggested by the author (equation 94).



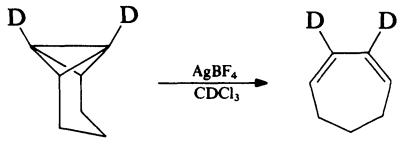
(94)

The preferential affinity toward the cleavage of these specific two bonds over the three other combinations probably stems from a steric effect.

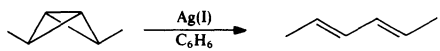
F. Transition Metal Promoted Rearrangements

As early as 1967 it was recognized that transition metals induce a facile rearrangement of carbon compounds containing strained sigma bonds. This observation had an immense impact on the chemistry of bicyclobutane as is reflected by the burst of publications on this subject especially in the years 1971–72. The attractiveness of this field is probably due to the fact that it combined three frontiers of the chemistry which were rapidly developing in the later 1960s and early 1970s, namely, the chemistry of small-ring compounds, organometallic chemistry and the application of orbital symmetry rules.

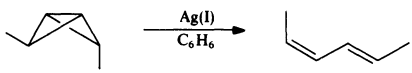
In most cases the products obtained are derivatives of 1,3-butadiene. Although in this respect the reactions resemble the thermolyses of bicyclobutane, there are two major differences between these two classes of reactions. The first one lies in the reaction conditions. While the thermal reactions necessitate elevated temperatures and are characterized by high activation energies (see Section V.G) most of the reactions with transition metals occur very rapidly at room temperature. The second difference is in the stereochemistry of the reaction. While thermal reactions (be they concerted or not) generally follow the Woodward–Hoffmann rules, transition metal promoted reactions give products with a different stereochemistry. These can be formally viewed as $2\sigma + 2\sigma$ processes. The following reactions illustrate this point (equations 95–97). Further labeling



(Ref. 210) (95)



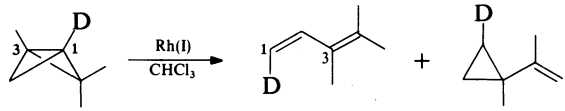
(Ref. 211) (96)



(Ref. 211) (97)

of the substrate showed that not only is the stereochemistry of the metal catalyzed reaction different but also these reactions differ from thermolysis reactions in that the central bond is not retained in the product (equation 98)[212,213].

The nature of the reactions is very complex. As will be shown, the reaction modes depend

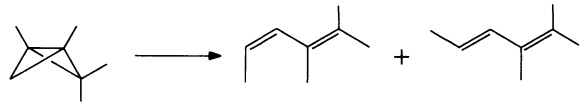


(98)

at least on four different parameters. These are: the substituents on the substrate, the identity of the transition metal, its ligands and the reaction medium. Examples of how these affect the reaction products will be briefly reviewed in the following paragraphs.

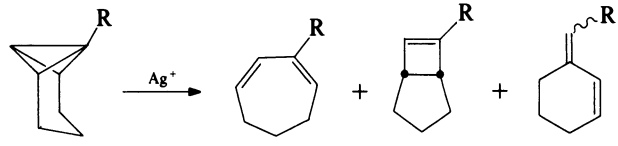
1. Substituent effect

As was shown in the preceding section, 1,2,2-trimethylbicyclobutane decomposes to give the corresponding butadiene and vinylcyclopropane. Addition of a methyl group at the second bridgehead position effects a loss of the stereospecificity, as shown by the fact that the two dienes were obtained in a nearly 1:1 ratio (equation 99)[214]. In addition, no vinylcyclopropane was observed.



(99)

Another example is the reaction of **70** with silver ions (equation 100) which emphasizes the steric effect of the substituent[215]. The increase in the size of the substituent R drastically affects the product distribution.

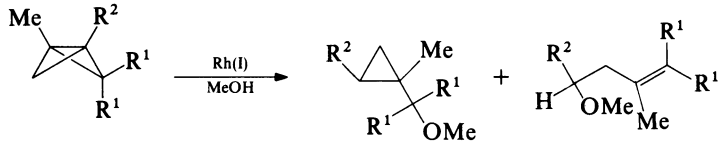


(100)

(70)

R = H	100%		
R = Me	26%	44%	29%
R = *t*-Bu	4%	92%	

When the reaction of **71** was performed in MeOH, compounds **72** and **73** were obtained (equation 101)[216]. For R^1 = Me, R^2 = H, only **72** was obtained. For R^1 = Ph, R^2 = H, a



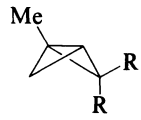
(101)

(71) **(72)** **(73)**

mixture of **72** and **73** was obtained whereas for R^1 = Ph and R^2 = Me, **73** was the sole product.

Relevant to substituent effects is the reaction of a chiral Rh(I) reagent with enantiomeric

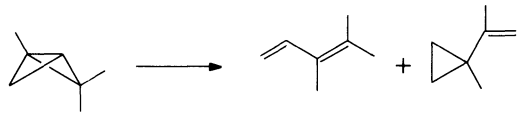
mixture of **74**. With R = Me only a small enrichment of one of the enantiomers was observed. However with R = Ph an enantiomeric excess of over 30% was obtained after 60% conversion[217].



(74)

2. *Metal effect*

There are quite a few comparative studies in this field[218–222] and the most extensive ones come from Gassman's group[223, 224]. The effect of the metals on the reactions depicted in equation 102 is presented in Table 2.

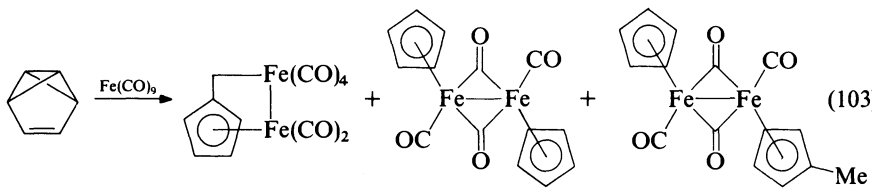


(33) (75) (76) (102)

TABLE 2. Transition metal promoted isomerization of 1,2,2-trimethylbicyclobutane (**33**) to **75** and **76** in $CHCl_3$[224]

Catalyst	75(%)	76(%)
$Co(CO)_8$	24	42
$Cu(BF_4)_2 : 6H_2O$	—	43
$Mn_2(CO)_{10}$	12	22
$HgBr_2$	—	58
$(PhCN)_2PdCl_2$	29	5
$[Rh(CO)_2Cl]_2$	58	30
$Ru_3(CO)_{12}$	30	38
$[Ru(CO)_3Cl_2]_2$	59	24
$RuCl_3$	26	49
$SnCl_2$	—	62
ZnI_2	—	71
$Zn(BF_4)_2$	—	54

A most unusual reaction was observed in the case of the iron nonacarbonyl promoted decomposition of benzvalene (equation 103)[225]. In this exceptional reaction, carbon is



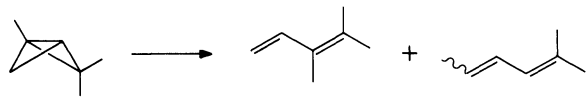
(103)

two isomers

eliminated from the ring skeleton. The stability of the biscyclopentadienyl complex was suggested to be the driving force of the reaction[225].

3. Ligand effect

The significance of the metal ligands in the course of the reaction can be inferred from the data already presented in Table 2 where, in some cases, results were reported for the same metals with different ligands. Further manifestation of the ligand effect is provided by the reaction of **33** with Pd(II)[226] (equation 104, Table 3).



(104)

(33) **(75)** **(77)**

TABLE 3. Ligand effect on the isomerization of 1,2,2-trimethylbicyclobutane[226]

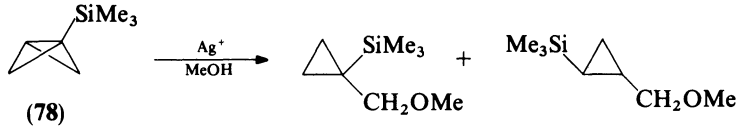
Catalyst[a]	75(%)	77(%)
$PdCl_2(PhCN)_2$	20	80
$PdCl_2(Ph_3P)_2$	60	40
$PdCl_2(Ph_3As)_2$	30	70
$PdCl_2Py_2$	15	85

[a] ca. 0.3 mol%.

4. Solvent effect

This subject has been less systematically studied. However, it is clear that such an effect does exist. The following are examples of this effect.

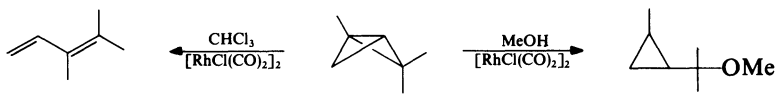
It was found[227] that **78** is inert to $AgClO_4$ (and also to TsOH) in benzene. On the other hand, when the reaction was performed in MeOH[228], two products (equation 105) were obtained in a 1:1 ratio.



(105)

(78)

Another example of the difference between MeOH and an aprotic solvent is the reaction of **33** with $[RhCl(CO)_2]_2$. In MeOH the reaction resulted in the formation of **79**[216], while in $CHCl_3$ the diene **75** was obtained (equation 106)[229].



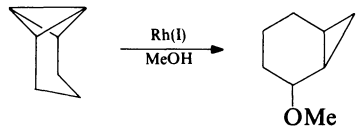
(106)

(75) **(33)** **(79)**

5. Reaction mechanism

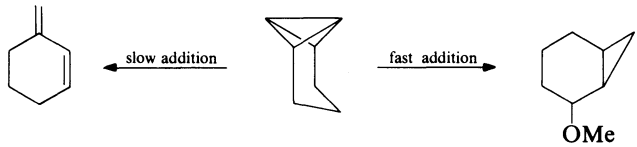
The previous discussion clearly shows that there are at least four parameters that can affect the course of the reaction. Thus, a complete description of the reactions of bicyclobutane with transition metals must entail a complete mapping of the four dimensional (substituents, metals, ligands and solvents) surface. The data available indicate that only partial mapping of selected narrow zones on this surface has been performed. Thus a complete picture and a unified view are still lacking.

The situation is in fact far more complex, since in addition to the four reaction parameters mentioned above, the experimental conditions were found to be of primary importance in determining the reaction course. This is demonstrated in the reaction of bicyclobutanes with transition metals in MeOH. It was reported[230,231] that interception of the intermediate by the solvent leads to the formation of an ether (equation 107). A



(7) (80) (107)

similar reaction was studied by Dauben and Kielbania[232] who reported that ethers were indeed formed, but only when an aged solution of the rhodium catalyst was employed. It was suggested, therefore, that the addition of MeOH is catalyzed by the acid present in the aged rhodium solutions[232a]. Reinvestigation of the reactions in MeOH was reported by Gassman and Reitz who did not find any aging effect. However, they found instead an extremely interesting effect. When substrate **7** was added to a Rh(I) solution in MeOH, a drop in the pH of the solution was indeed observed. Moreover, the rate by which the substrate was added had a large effect on the course of the reaction. When **7** was rapidly added to a vigorously stirred solution of Rh(I) in MeOH, **81** was obtained in a 6% and **80** in a 86% yield. Slow addition of **7** results in the formation of 76% **81** and only traces of **80** (equation 108). When the reaction was conducted in the presence of $NaHCO_3$, 90% yield of **81** and only 10% of **80** were obtained[232b].



(81) (7) (80) (108)

Since neither Rh(I) nor **7** when dissolved separately in MeOH yield acidic solutions, it is clear that the acid is generated by the encounter of the two species. A rationale for this behavior was put forward by Dauben and Kielbania[233]. On the basis of changes observed in the absorption of the metal CO ligands in the IR spectrum, it was suggested that a MeOH molecule nucleophilically attacks the carbonyl group releasing H^+ in the second step. However, it should be recalled that acidification of the solution was also observed upon the interaction of $AgClO_4$ and the substrate[234]. Obviously, in this case, another explanation must be sought.

Based on careful studies[231,235], it seems that in addition to the acid-catalyzed reactions in MeOH, transition metals can by themselves induce the formation of ethers.

In addition to complications due to the intervention of acid catalysis and the effect of substrate addition mode on the reaction course, it was found that the amount of catalyst used also has an important role in the reaction[226]. Data for the reaction of **33** (equation 104) are presented in Table 4.

TABLE 4. Product distribution in the reaction of $PdCl_2(Ph_3As)_2$ with 1,2,2-trimethylbicyclobutane (**33**)[226]

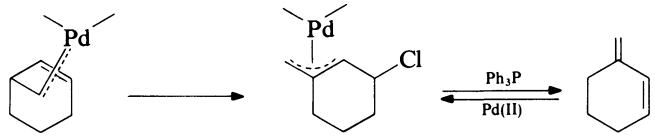
Catalyst (mol%)	**75**(%)	**77**(%)
0.3	30	70
1.5	60	40
3.0	100	—

The latter complication was explained by Gassman and coworkers who demonstrated that ligand exchange with the product leads to a new complex exhibiting a different selectivity from that of the original complex[224,236].

In light of all this, it is not surprising that Bishop in his review on transition metal promoted rearrangement of small-ring compounds[4] concludes: 'No class of transition metal catalyzed rearrangements has been the subject of more controversy than those of bicyclobutane.'

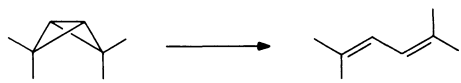
Despite the confusion and controversy some mechanistic generalizations can be made. For example, it is now apparent that these reactions are not concerted. Supporting evidence is obtained from different sources such as NMR product analysis, kinetics, trapping experiments and in rare cases even the isolation of intermediates.

The first spectral observation of intermediates in the reaction of bicyclobutane with transition metals was simultaneously reported by the groups of Masamune[237] and Dauben[232a]. Using equivalent amounts of $PdCl_2(PhCN)_2$ and **7** they were able to observe an intermediate (**82**) which was further converted to the π-allyl complex **83** (equation 109). Treatment of this complex with Ph_3P gave **81**.



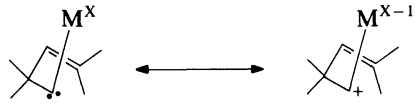
(82) (83) (81) (109)

The isolation of a vinylcyclopropane in the reaction of **33** (equation 102) indicates that the reaction involves two stages. The first is cleavage of a side bond, which may later be followed by cleavage of the central one[213]. The process involves a migration of hydrogen from C(4) to C(3). When C(4) is substituted by two methyl groups as in **84**, **85** is obtained



(84) (85) (110)

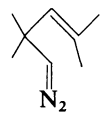
(equation 110). It was suggested that the intermediate is **86** (equation 111) and that its formation is followed in this case by a migration of a vinyl group[213].



(111)

(86)

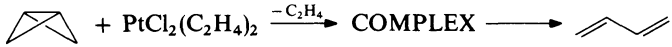
Supportive evidence for the identity of intermediate **86** was also obtained from the transition metal promoted reaction of the corresponding diazo derivative **87** which furnished the same product[214, 218].



(87)

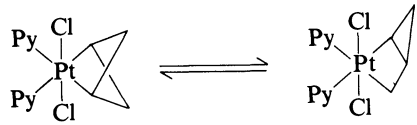
A kinetic indication for the intermediacy of a substrate–transition metal complex was obtained in the reaction of 2,4-dimethylbicyclobutane with Ag^+. The reaction order in the substrate was found to be dependent on the initial concentration of the substrate. As the concentration of the substrate is increased, it gradually changes from unity towards zero[230]. Such a saturation effect is typical of a reaction in which an intermediate is formed.

Finally, an organometallic intermediate was actually isolated from the reaction of bicyclobutane with Pt(II) (equation 112)[239].



(112)

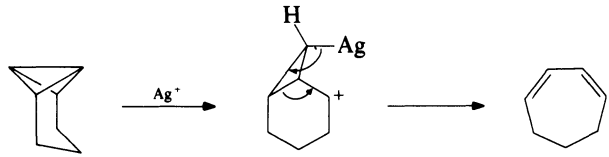
Due to experimental difficulties, the structure of this complex was not determined. However, when reacted with pyridine, complex **88** was obtained and found to equilibrate in solution with **89** (equation 113).



(113)

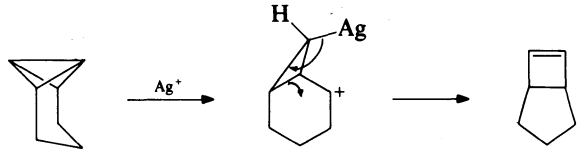
(88) **(89)**

The silver-catalyzed reactions of bicyclobutanea were thoroughly studied by Paquette's group. They showed that in some cases, the reaction sequence involves first cleavage of a side bond to form an argentocarbocation, which is then followed by a skeletal rearrangement[240]. Two examples are shown below (equations 114 and 115). (For the last



(114)

(7)

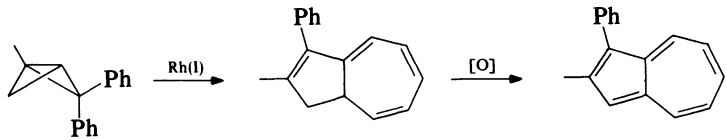


(115)

(7)

reaction, the authors described the intermediate using a three-center non-classical bonding[240], which, for sake of simplicity has been replaced by a classical structure in equation 115). Interestingly a kinetic isotope effect k_H/k_D of 1.74 was found for the reaction described in equation 115. However, the origin of this effect is not clear[241, 242].

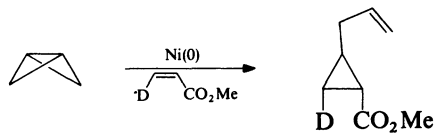
One of the intermediates of the reaction of bicyclobutane with transition metals is a resonance hybrid of two structures shown above (**86**). The carbene nature of this intermediate derives strong support from both inter- and intramolecular trapping experiments. An example of the former is the formation of the azulene precursor **90** in the following reaction (equation 116)[222, 229]. The formation of **90** is best explained by a carbenoid insertion into a phenyl ring.



(116)

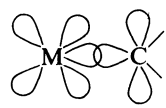
(90)

When the reaction of bicyclobutane with Ni(0) was performed by using methyl acrylate as a solvent, an insertion into the electrophilic double bond took place yielding cyclopropyl derivatives (equation 117)[243–245].



(117)

A rationale for the behavior of the various intermediates was put forward by Noyori[246]. The bonding between the metal and a σ carbene can be best represented by **91**. The σ lone



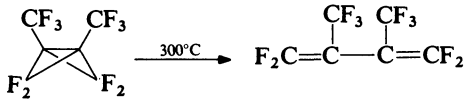
(91)

pair in the carbene is donated into the vacant orbital of M forming a σ bond. Back-donation from a d orbital into the vacant p orbital of the carbene forms a π bond. Thus, the degree of donation–back-donation determines the ionic character of the metal–carbene bond. Ag is a poor π donor and therefore it tends to form carbocations. Rh(I), Ir(I) and Pd(II) are more electronegative than carbon, therefore their carbenoids undergo typical carbenoid reactions. On the other hand, Ni(0) is more electropositive and its carbenoid therefore exhibits characteristic nucleophilic behavior.

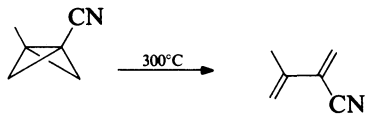
G. Thermal Reactions

1. Rearrangement

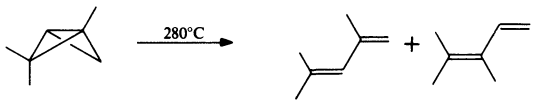
In most cases, thermolysis of bicyclobutane derivatives yields compounds containing a 1,3-butadiene moiety. Substituents originally located at the bridgehead position assume positions 2 and 3 in the butadiene product, indicating that in the course of the reaction the central bond remains intact. Selected examples are given in equations 118–121.



(ref. 130) (118)

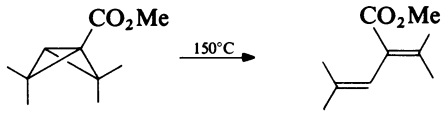


(Ref. 104) (119)



48% 52%

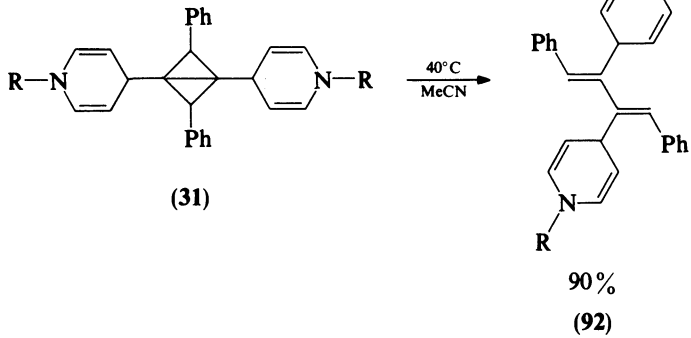
(Ref. 87) (120)



(Ref. 106) (121)

While most of the reactions necessitate elevated temperatures, there is an interesting case where 'thermal' conversion occurs at a relatively low temperature. Thus, **31** is converted to the diene **92** at 40°C with a half-life of only 45 minutes (equation 122)[128].

Another interesting feature of the reaction lies in its stereochemistry. This is best illustrated by the work of Closs and Pfeffer[247] who studied the pyrolysis of the two



(31)

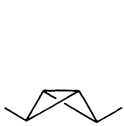
90%

(92)

(122)

stereoisomers **93** and **94**. The results presented in Table 5 show that diene formation is largely stereoselective although not stereospecific.

TABLE 5. Stereoselectivity in the thermal reactions of **93** and **94**[247]

Compound	Yields (%)			
 **(93)**	3.9	93.2	2.9	—
 **(94)**	95	1.2	2.2	1.6

Mechanistically, two conceivable pathways can be envisioned for the reaction. The first is a concerted $\sigma 2s + \sigma 2a$ process which, according to the Woodward–Hoffmann rules[176] is an 'allowed' reaction. The other one is a stepwise reaction in which one of the side bonds is homolytically cleaved in the rate-determining step (equation 123).

 (123)

The Woodward–Hoffmann rules predict that thermolysis of an *exo–exo* or *endo–endo* 2,4-disubstituted bicyclobutane will result in the formation of a *cis–trans* disubstituted butadiene, whereas *endo–exo* substitution will lead to the formation of a *trans–trans* butadiene. The data presented in Table 5 show that to a large extent the thermolysis of compounds **93** and **94** does indeed display a steric course which is in accordance with the Woodward–Hoffmann rules.

In order to explain the stereochemical results in terms of the diradical mechanism, one must assume that the diradical intermediates collapse to dienes before rotamer equilibration is achieved. This demand led to the conclusion[247] that the concerted mechanism accommodates the results with less stringent demands. Thermochemical calculations[100] provide additional support for the conclusion that there is only a small probability for a diradical pathway.

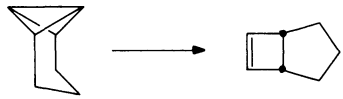
A diradical pathway was suggested by Christl and coworkers[248] for **95** (equation 124). This is supported by the lower activation energy for this compound as compared with its analog, **7**, whose diradical intermediate is a less potent radical stabilizer (equation 125).

The conclusion that bicyclobutane undergoes a thermal concerted rearrangement to butadiene was challenged by Dewar and Kirschner[249]. Using MINDO/3 calculations, they showed that the activation energy for a fully concerted (symmetric) transition state is ca. 90 kcal mol^{-1}. This is approximately the sum of the activation energies for the cleavage of two peripheral C–C bonds. Employing CI in the calculation shows that the reaction follows the diradical course with an activation energy of 40 kcal mol^{-1} which is in perfect agreement with the experimentally determined value[250,251]. The calculated activation

ΔH^*(kcal mol^{-1})

31.5 (124)

(95)



37.9 (125)

(7)

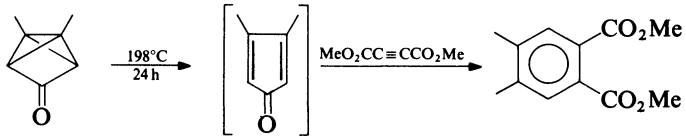
energy for an interconversion of two radical rotamers was determined to be 8 kcal mol^{-1}. Thus a high stereoselectivity does not necessarily argue against a stepwise reaction.

On the other hand MINDO/3 calculations[249] reveal that the conversion of benzvalene to benzene (equation 126) is thermally allowed. It is worth noting that according to the calculations, the transition state of this reaction is highly asymmetric. For example, the two side bonds which are cleaved during the course of the reaction have lengths of 1.601 and 2.100 Å. Thus the term 'concerted' in this case does not imply an identical degree of progress for all of the processes in the transition state.

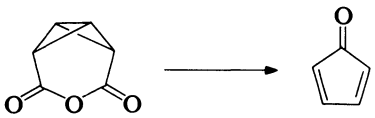
(126)

Experimental support for this concertedness of the reaction was provided by Turro, Katz, Wiberg and coworkers[252]. They found that, unlike the reaction of Dewar benzene, the reaction of benzvalene is not chemiluminescent, although energetic considerations show that the energy released in the reaction (activation enthalpy 26 kcal mol^{-1} and reaction enthalpy 67 kcal mol^{-1}) is well above the energy required to form the benzene triplet (82 kcal mol^{-1}). This argues for a concerted reaction, in which a strongly avoided crossing between the ground state and an excited state surfaces is to be expected[253].

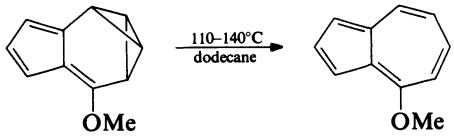
Thus, in conclusion, the concertedness of a reaction is not self-evident even when its steric course is in accordance with that predicted by the Woodward–Hoffmann rules. It seems therefore that in general, an unambiguous mechanistic assignment is hard to obtain[146] and each case must be examined independently.



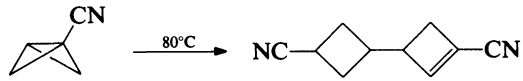
(Ref. 131) (127)



(Ref. 127) (128)



(Ref. 254) (129)

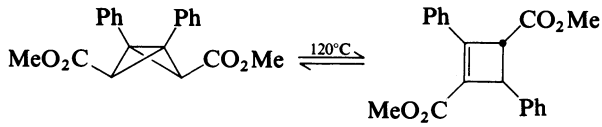


(Ref. 107) (130)

Equations 127–130 are several additional interesting examples of pyrolytic reactions of bicyclobutane derivatives.

2. *Isomerization*

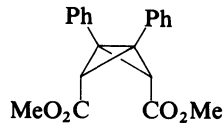
In the preceding discussion it was mentioned that the central bond remains intact during the course of the thermal reaction. There is, however, another thermal reaction which is associated with the central bond. In 1966, Dyakonov and coworkers reported the following equilibrium (equation 131)[255]. Three years later it was shown[52,256] that the



(131)

(6c)

cyclobutene structure was mistakenly assigned to the compound in equilibrium with **6c**. In fact, **6c** equilibrates with its *endo–endo* isomer **6a**. For such a process to occur the central



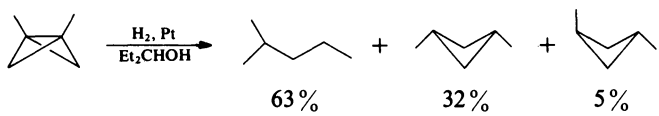
(6a)

bond must be considerably weakened. It seems therefore that the *endo–exo* isomerization rate is governed largely by the substituents at the bridgehead positions. Phenyl and probably other radical stabilizing substituents are likely to enhance *endo–exo* isomerization more than conversion to dienes.

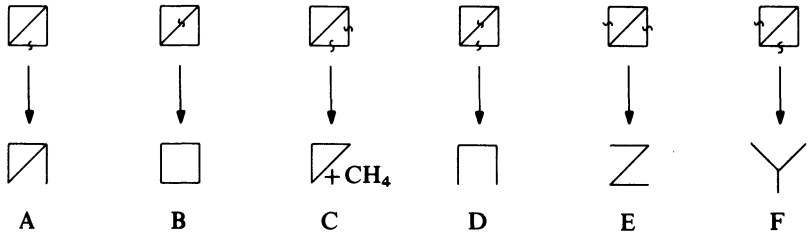
Theoretical aspects of this reaction are discussed in Section II.G.

H. Hydrogenation

Compared to many other hydrocarbons, bicyclobutane derivatives undergo a relatively facile hydrogenation reaction. Depending on substituents and reaction conditions, one or two moles of hydrogen can be absorbed. This is exemplified in equation 132[153].

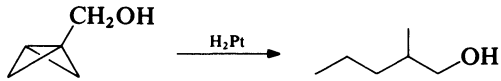


(132)



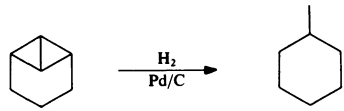
SCHEME 1

Scheme 1 shows the formal possibilities for hydrogenolysis of one and two bonds in bicyclobutane. Since in no case were products containing a cyclopropane ring obtained and since under the conditions employed cyclopropanes are usually inert to hydrogenation, modes A and C remain only formal possibilities. Mode B can be easily identified since it is the only one which leads to a cyclobutane product. However, in cases where a suitable substitution pattern is absent, it is practically impossible to distinguish between modes D and E. Thus the following reaction (equation 133)[65] can comply with both the

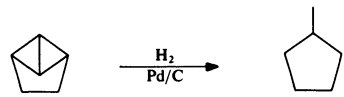


(133)

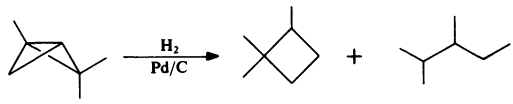
D and E modes. The following two reactions (equations 134, 135) could in principle follow the D and F modes. A reaction which can be considered to result from all three modes, D, E and F was reported by Skattebol (equation 136)[87].



(Ref. 95) (134)

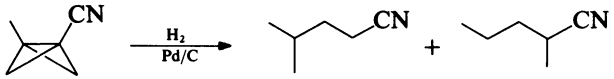


(Ref. 138) (135)

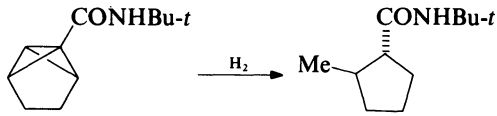


78% 22% (136)

Data gathered from reactions in which two moles of hydrogen are absorbed have provided evidence only for the existence of modes D and E. Mode D can be assigned to the reactions of equations 137 and 138. On the other hand the reaction of **20** in which

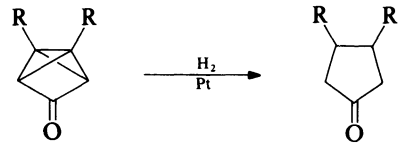


79% 2% (Ref. 104) (137)



(Ref. 112) (138)

R = Me[131] or Ph[132] follows mode E (equation 139). There is yet no case for which mode F can be unambiguously assigned. We note that all these conclusions obviously do not consider the possibility of skeletal rearrangements.

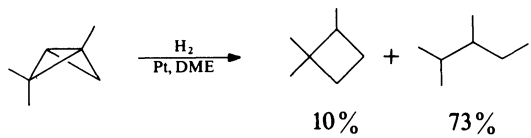


(139)

(20)

In cases where two bonds are cleaved, it is often suggested that the cleavage occurs in one step. This assumption is based on the fact that a stepwise reaction would lead to the formation of either cyclopropyl or cyclobutyl derivatives which are usually inert under the conditions employed. However, it is well established that the pervasive hydrogen species chemisorbed on transition metal surfaces is the hydrogen atom[257,258]. Thus the mechanism could still be stepwise since the cyclic intermediates are obtained as highly reactive radicals which can further add hydrogen in a series of successive steps.

It is difficult to predict *a priori* the direction of the reaction, since its actual course may be affected by many parameters. Among these are the nature of the catalyst, the geometry of the substrate adsorption on the surface, the density of the adsorbed H atoms etc. One of the reactions mentioned above (equation 136) which was performed in MeOH can serve as an example of the effect of the conditions on product distribution. A change in catalyst and solvent inflicted a drastic change in the ratio of the products (equation 140).



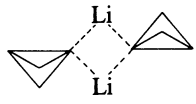
(140)

Since two bonds are cleaved in the majority of the catalytic hydrogenation reactions, a method to cleave the central bond exclusively is desired. Such a method was discovered by Moore and coworkers who reported that for eleven different bicyclobutanes, specific reduction of the central bond was achieved by refluxing the substrate with Li in $EtNH_2$. The reaction is not stereospecific and the two isomers of the substituted cyclobutane are obtained[259].

I. Deprotonation Reactions

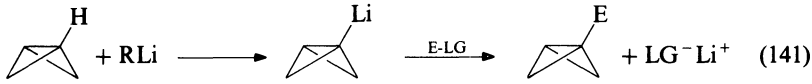
Already in the early stages of its study, it was found that bicyclobutane can undergo deprotonation reaction at a bridgehead position[112]. The relatively high acidity of bicyclobutane was ascribed by Closs and Larrabee[59] to the high s character in this C–H bond. This is reflected in the large J_{C-H} value of the bridgehead proton. In a series of tricyclic compounds containing the bicyclobutane moiety, a rough correlation was indeed observed between the J_{C-H} (i.e. s character) and the deprotonation rate constants[59] (see Section III).

The lithium salts of bicyclobutane derivatives are relatively stable. X-ray analysis of lithium bicyclobutane prepared in the presence of *N,N,N',N'*-tetramethylethylenediamine showed that the salt exists as a dimer having structure **96**[260].



(96)

The deprotonation reaction provides a valuable route for the introduction of a variety of groups into the bridgehead position. The scheme of the general procedure is outlined in equation 141.



(141)

E = electrophile; LG = nucleofuge

Employing this technique, groups E such as CO_2H[261], CO_2Me[262], Me[261], silyl[227, 263], MeS[123, 264], and CN, Cl, Br, I, MeSe[264] were introduced, generally in good yields, into the bridgehead position.

J. Polymerization

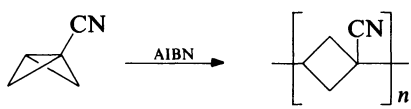
In light of the similarity between the bridge bond in bicyclobutanes and the π bond in olefins, it is not surprising that bicyclobutanes undergo relatively facile polymerization. In fact, in many cases it is highly recommended to store bicyclobutane derivatives either below $-50°C$ or with radical inhibitors to prevent undesired polymerization. The majority of the data in the literature relates to radical polymerization reactions. While anionic polymerization has been observed, it seems that bicyclobutanes in general do not undergo effective cationic polymerization.

1. Radical polymerization

In principle, bridgehead substituents can be electron-withdrawing, alkyl, or elecron-donating groups. Examples of the latter are rare; they are generally unstable and their ability to participate in polymerization reactions has not been investigated.

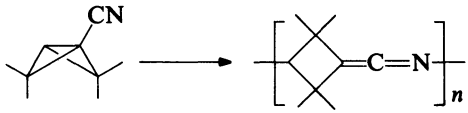
Among the other two groups, only bicyclobutanes with electron-withdrawing substituent at the bridgehead position undergo radical polymerization[105]. Bicyclobutanes with bridgehead alkyl groups do not polymerize[3] Thus, for example, Wiberg[65] found that methyl bicyclobutanecarboxylate, polymerizes rapidly under radical conditions to give a polyacrylate-like polymer whereas bicyclobutane itself does not polymerize.

Most of the studies have been performed on bicyclobutanecarbonitrile (equation 142) which polymerizes at a rate similar to that of acrylonitrile. High molecular weight polymers are obtained in this reaction[107]. Substitution of an alkyl group at the second



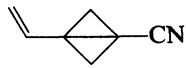
(142)

bridgehead carbon retards the reaction[105]. It is interesting to note that the nitrile group participates in the polymerization when the methylene bridge is substituted with methyl groups (equation 143)[107].



(143)

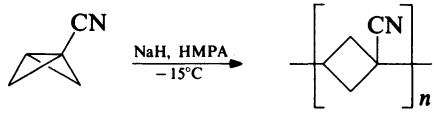
A butadiene analog (**97**) was prepared by Hall and Yancy[265] and found to polymerize readily when exposed to air or light.



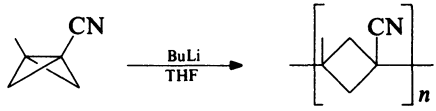
(**97**)

2. *Anionic polymerization*

One of the characteristic features of this type of polymerization is the relatively low molecular weight of the products. Catalysts such as NaH and BuLi are generally employed in these reactions[107] (equations 144 and 145). In contradistinction to radical polymerizations, addition of methyl at the second bridgehead position increases both the yields and the degree of polymerization[107].



(144)



(145)

3. *Cationic polymerization*

Although bicyclobutanes readily undergo electrophilic additions they do not seem to polymerize by cationic initiators. An exception was observed by Olah and Lukas[266] who reported that bicyclobutane polymerizes when dissolved in magic acid.

4. *Copolymerization*

Bicyclobutanes activated by bridgehead cyano group undergo copolymerization with various monomers such as vinyl chloride, acrylamide, acrylonitrile and styrene[3, 107].

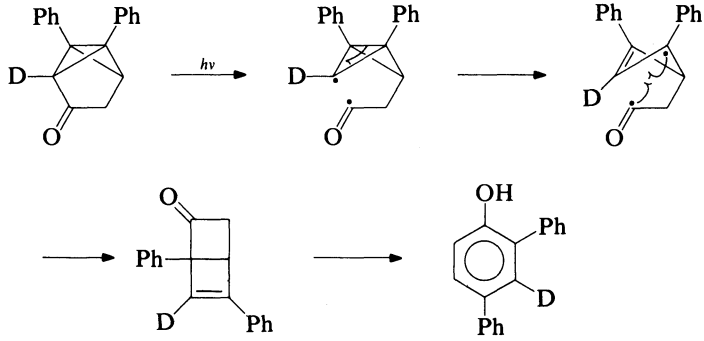
The relative reactivity of substituted bicyclobutanes toward polystyryl radical was determined by Hall and found to be smaller than that of common vinyl monomers[267].

K. Photochemistry of Bicyclobutane

The photochemistry of bicyclobutane has not been extensively studied. One of the major reasons for this probably lies in the fact that λ_{max} of bicyclobutane and most of its

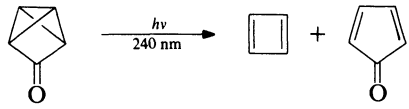
alkyl derivatives is below 200 nm. As a result, it reacts to irradiation only when properly substituted with chromophores. (Cases where it reacts with other excited species were discussed in Section V.D.)

Masamune and coworkers[268] observed the following interesting reaction (equation 146). The mechanism suggested was based mainly on the absence of scrambling of the deuterium atom in the product.



(146)

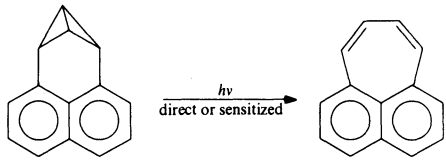
In an attempt to prepare tetrahedrane, Maier and coworkers irradiated **20**(R = H) in a matrix. However, this goal has not been achieved; instead, two other products were obtained (equation 147)[269].



(147)

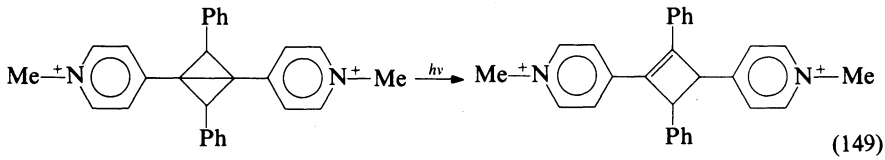
(**20**, R = H)

A symmetry-allowed photochemical ring-opening of bicyclobutane was reported by Pagni and coworkers (equation 148)[146]. This reaction was assumed to take place from the S_1 as well as from the T_1 states.



(148)

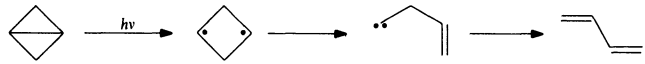
Photolytic cleavage of the central bond was reported by Horner and Hunig[62]. This reaction is followed by a 1,2-hydrogen shift to produce **98** (equation 149).



(149)

(**98**)

The first case where unsubstituted bicyclobutane was directly irradiated has only recently been reported[270]. Under irradiation at 185 nm, butadiene is obtained in 90% yield. Two mechanisms were suggested for this reaction. The first (equation 150) involves a homolytic cleavage of the central bond to the diradical species **99** whereas in the second (equation 151), the central bond remains intact.



(150)

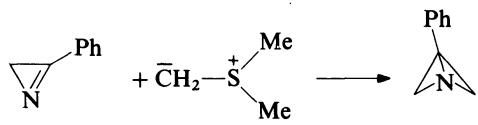
(99)

(151)

Extensive labeling experiments indicated that both mechanisms operate simultaneously with a ratio of 2:1 respectively. The results suggest that there are two excited states close in energy: one with a strong bridge bond and one with strong side bonds[270].

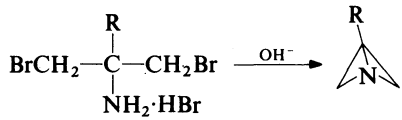
VI. HETEROBICYCLOBUTANES

The chemistry of bicyclobutanes in which one or more of the skeletal carbons is replaced by a heteroatom has not been explored to a significant extent. Probably the best known example is the bridgehead aza-derivative, which has been synthesized by two different methods. In 1967 Hortmann and Robertson[271] obtained this compound by adding dimethylsulfonium methylide to 2-phenylaziridine (equation 152). Using a different



(152)

method (equation 153), Funke[272] obtained the unsubstituted azabicyclobutane as well as its methyl and ethyl bridgehead derivatives.

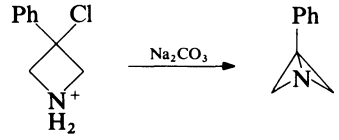


(153)

R = H, Me, Et

Azabicyclobutanes are, relatively speaking, highly electrophilic. They readily add Bronsted as well as Lewis acids across the central bond[273, 274]. Kurz and coworkers found that with phenyl at the bridgehead, the molecule adds HCl with a rate constant of $2.6 \times 10^6\ M^{-1}\,s^{-1}$. On the basis of additional mechanistic studies, they concluded that the protonation step is reversible[275]. The product of this reaction (**100**), rapidly ($t_{1/2} < 1$ s) eliminates HCl under basic conditions, reconstructing the central bond (equation 154)[275].

Replacement of the two methylene units in bicyclobutane by π-acceptor groups such as C=CH$_2$, C=NH, C=O, BH, BNH$_2$ results in the formation of a novel class of compounds. These compounds, most of which were only calculationally realized, belong to the Huckel



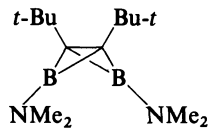
(154)

(100)

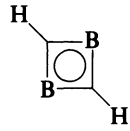
$4n+2$ aromatic series. Although they enjoy a larger π stabilization in a planar form, they were all found to be highly puckered[13,276,277]. Insertion of a π-acceptor group leads to elongation of the central bond. This effect becomes more pronounced as the electronegativity of the group increases. It reaches a maximum (1.75 Å at STO-3G, 1.86 Å at 4-31G[276] and 1.967 Å at GVB/3-21G[13]) with the diboretene **101**. Derivatives of this compound have

(101)

been synthesized[270–280], and the X-ray diffraction of **102** reveals a C–C distance of 1.814 Å and a high degree of puckering[279]. In fact, such a large separation of the two carbon atoms is more compatible with an aromatic formulation such as **103**, than with one in which the



(102)

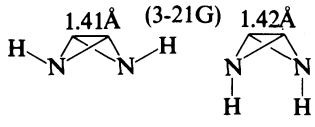


(103)

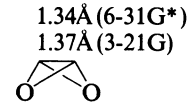
central bond is retained. Indeed, the aromaticity of **103**, although dependent upon the selection of the reference compound, was calculated to be very high (58 kcal mol^{-1})[13].

One of the major reasons for the puckering observed is the overlap population. This was found to be -0.23 in the planar structure of the diboretene **101** and only -0.04 in its puckered form[276].

While placement of π-acceptors at the 2 and 4 positions of bicyclobutane causes elongation of the central bond, calculations show that using nitrogen (**104**) leads to a bond shortening. A much more dramatic effect is observed with oxygen (**104a**)[281].



(104)



(104a)

The remarkable correlation observed between the theoretical predictions and the experimental structure determinations as demonstrated in the boretene case, lends much credibility to the theoretical methods. Since some of the molecules mentioned in this section have not been synthesized yet, it remains to be seen whether future experiments will strengthen further the reliability of these methods.

VII. BICYCLOBUTA-1(3)ENE

A. Theoretical Background

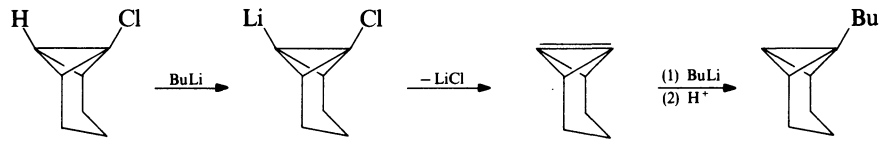
In an extensive search made by Hehre and Pople on the possible variations of C_4H_4 compounds, **105** was identified as one of the least stable isomers[282].

(105)

One of the characteristic features of this molecule was found to be its deviation from planarity. The interflap angle of its fully STO-3G optimized structure was found to be 128.3° [283]. This result is somewhat surprising since it is not immediately clear why this olefin should be distorted from a planar D_{2h} to a puckered C_{2v} symmetry. An explanation was offered by Wagner, Schleyer and coworkers[283] who studied the energy of ethylene as a function of geometrical distortions. It was found that as the HCC angle becomes smaller than 100°, the hydrogens start to deviate from the original plane of the molecule. This deviation from planarity enables the C–H bonds to overlap with the pure π orbital and thereby stabilize this conformation.

B. Preparation and Mechanism

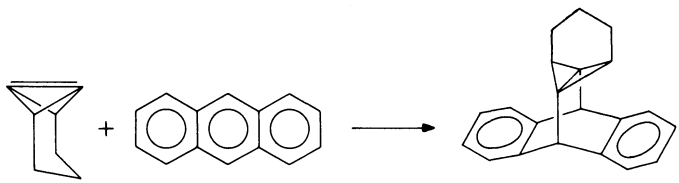
Only two years after the suggestion that there is only a remote possibility of detecting **105**, the first experimental evidence for its existence as an unstable intermediate was reported[284]. Szeimies and coworkers reacted 1-chlorotricyclo[4.1.0.$0^{2,7}$]heptane (**106**) with BuLi and obtained the substitution product **107**[284]. The mechanism suggested was an E1cB elimination of HCl to form **108** which adds BuLi in the next step (equation 155).



(106) **(108)** **(107)**

(155)

Three types of evidence in favor of this mechanism as opposed to a metal–halogen exchange or direct coupling have been given: (1) the first formed carbanion was trapped by D_2O; (2) no reaction was observed when the hydrogen at the bridgehead was replaced by a methyl group[284]; and (3) **108** was trapped by anthracene in a Diels–Alder reaction giving **109** (equation 156)[285].



(108) **(109)**

(156)

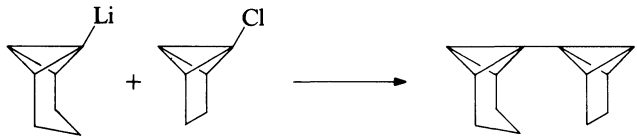
Competition experiments with two dienes and **108** gave identical product distribution irrespective of the identity of the halogen in the starting material[286]. This result provides additional support for the suggested mechanism.

The HCl elimination method was also utilized in preparing the hitherto unknown C_6H_6 isomer **110**, which differs from benzvalene in the location of the double bond[287a]. It is worth noting, however, that attempts to synthesize **105** or its methyl derivative by this method were unsuccessful[287b].

(110)

C. Synthetic Applications

Since the base which induces the elimination reaction can add at a later stage across the double bond, bridgehead coupling of two bicyclobutanes can be induced by reacting the bridgehead lithium salt of one (acting as the base and the nucleophile) with the 1-chloro derivative of the other[287, 288] (equation 157). This, in general, is a synthetic route for bridgehead substitutions by highly basic nucleophiles[289].

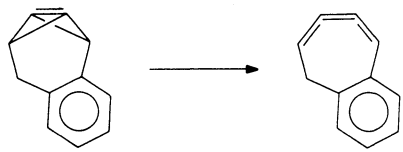


(157)

In order to introduce groups which cannot effect the elimination reaction, sterically hindered non-nucleophilic bases such as lithium diisopropylamide[290], lithium 2,2,4,4-tetramethylpiperidide[285] or even *t*-BuO^-[286] can be used. Employing this technique, Szeimies and coworkers introduced thio and amino groups into the bridgehead position of bicyclobutane derivatives[291, 292].

The Diels–Alder reaction of **108** and its analogs with other dienes such as furan[290] and benzindole[293] derivatives has been demonstrated as a valuable route to small-ring propellanes containing the bicyclobutane moiety[292]. The interesting chemistry of these propellanes was also investigated[294] but it is beyond the scope of this chapter.

Several other derivatives of **105** were prepared[295]. Among these is **111** which was found to undergo partial isomerization to **112** above 20°, (equation 158).



(158)

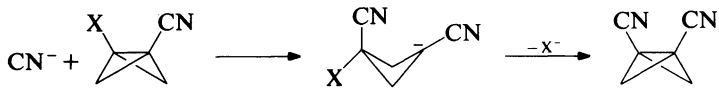
(111) **(112)**

VIII. IONIC BICYCLOBUTANE

Ionic bicyclobutane can be described as a bicyclobutane in which the central covalent bond has been replaced by an ionic one. In other words, it is a cyclobutane in which positions 1

and 3 are oppositely charged. This interesting species was first observed by Hoz and Aurbach as an intermediate in the course of a nucleophilic reaction of alkoxides with 3-halobicyclobutanecarbonitrile (**113**)[296].

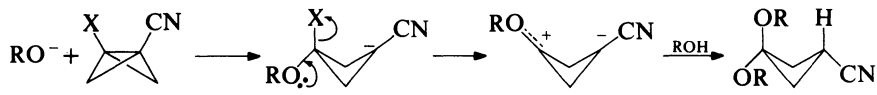
When a nucleophile such as CN^-, which lacks an appreciable positive mesomeric effect, reacts with this substrate, the expected addition–elimination mechanism is observed[190] (equation 159). However, when alkoxides are employed as nucleophiles, the reaction takes



(**113**)
X = Cl, Br

(159)

an entirely different course as shown in equation 160. In this case the positive and negative charges on the ionic bicyclobutane **114** are stabilized by alkoxy and cyano groups respectively[296].

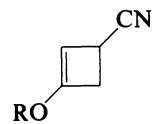


(**113**) (**115**) (**114**)
X = Cl, Br

(160)

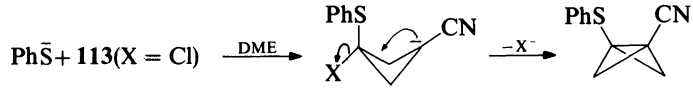
The crucial step in this mechanism is the second one in which the α-haloether moiety **115** solvolyzes to give an oxocarbocation. In order to obtain the ionic bicyclobutane this step has to compete effectively with both protonation of the carbanion and the 1,3-elimination reaction. By using oxygen nucleophiles, e.g. MeO^-, EtO^- and $CF_3CH_2O^-$, in protic solvents, the rate of these three reactions was found to decrease in the order: solvolysis > elimination > protonation. Although an apolar medium is expected to enhance the elimination reaction and to slow down the solvolytic step, it was shown that for MeO^- in THF, the ionic bicyclobutane route still prevails[296].

It is interesting to note that in this case a small amount (< 10%) of the olefin **116** is obtained. This provides the second known example for a fast deprotonation from an oxocarbocation[297] which usually does not undergo this reaction[298].



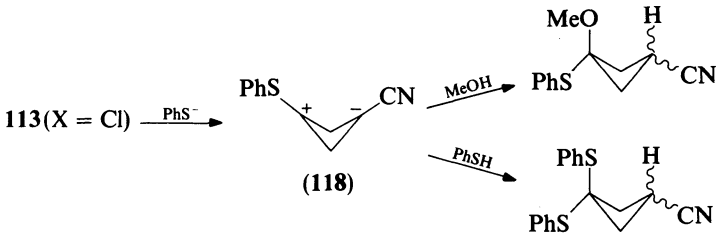
(**116**)

Since the expulsion of the leaving group is largely dependent on the mesomeric effect of the nucleophilic moiety incorporated in the molecule, one might expect that the use of thio nucleophiles should shift the mechanism to the addition–elimination mode. Indeed, when the reaction of **113** with thiophenoxide was performed in dimethoxyethane, the addition–elimination product **117** was exclusively obtained (equation 161)[299]. However, in methanol the ionic bicyclobutane mechanism was found to be operative in spite of the weaker mesomeric effect of the thio group (equation 162)[299].



(161)

(117)



(162)

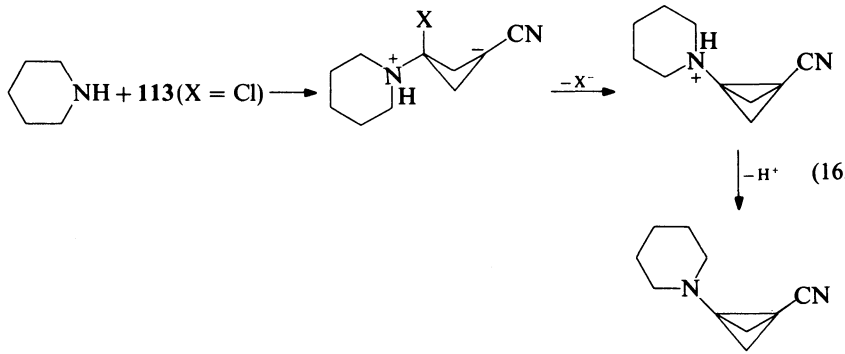
(118)

When **117** was exposed to the same reaction conditions in methanol, it was relatively very inert. This supports the assumption that **117** is not an intermediate in the reaction in methanol[299].

The polarity of the medium has a drastic effect on the mechanism of the reaction. Variations of the polarity obtained by adding methanol to DME, had no effect on the reaction course up to ca. 2.5 M of MeOH. The fraction of the elimination reaction then rises steeply, from 0.1 at 3 M to 0.5 at 6 M of MeOH[299]. Experiments with other solvent systems indicated that the shift in mechanism occurs at $E_T(30)$[300] values around 47[301].

The lifetime of the ionic bicyclobutane is a parameter of prime importance. An attempt was made to estimate this parameter for the thio-derivative using the clocking method[302]. The latter involves competition between two nucleophiles e.g., PhS^- and the solvent MeOH. Assuming that the PhS^- reacts with carbocations at a diffusion-controlled rate[303] and given the product ratio as a function of concentration, the lifetime of **118** in methanol was calculated to be of the order of 10^{-8} seconds[186].

Preliminary results indicate that the reaction of amino nucleophiles with **113** follow the addition–elimination mechanism[301]. This is because the nitrogen is quaternary in the crucial step and cannot make use of its mesomeric effect for a rapid expulsion of the leaving group (equation 163)[301].



(163)

Since cyclopropanes are known to cleave heterolytically in photochemical reactions, bicyclobutanecarbonitrile was photolyzed in methanol in an attempt to generate the ionic bicyclobutane via an alternative route[186]. However, this and other photochemical reactions of bicyclobutane derivatives (see Section V.K), yield no evidence of an ionic bicyclobutane.

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CHAPTER **20**

[m.n.1]Propellanes

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I. INTRODUCTION

In accord with editorial policy for this series, encyclopedic coverage of the subject matter is not sought. This is accepted pragmatically particularly since the reader who seeks a full list of references on [m.n.1]propellanes may obtain this in another place, albeit interspersed in the various chapters of the books cited[1-3].

I shall therefore discuss and assess the major aspects of the title compounds. The order in which I do so is arbitrary but there is method in my madness if free association may be deemed method.

Several important themes that come immediately to mind are associated (strongly bound, not freely) with the variegated interests of the organic chemist: theory, structure, mechanism and synthesis. The first two will be intimately interwoven in our discussion of small ring propellanes. Propellanes, in general, by virtue of their geometry have served as useful stereochemical models. We shall see how beautifully chosen propellanes containing a cyclopropane ring were studied in order to check whether or not an S_N2 reaction may take place at a saturated carbon in such a ring. We shall discuss the synthesis of [m.n.1]propellanes, solvolysis of certain examples, and the use of such compounds in the syntheses of alicyclic compounds with angular methyl groups.

The propellane nomenclature refers to tricyclic compounds or moieties in compounds in which there occur three rings with a common conjoining single carbon–carbon bond. The definition of propellanes disregards that conjoining bond and merely gives the additional number of atoms forming a particular ring. Thus, compound **2** contains a moiety composed of two cyclohexane rings and one cyclopropyl ring, this is a [4.4.1]propellane moiety. Were three cyclopropane rings conjoined in a single carbon–carbon bond, the compound would be named [1.1.1]propellane. In the first-mentioned moiety m = 4, n = 4; in the second m = 1. n = 1. Since we are dealing with chemistry of cyclopropanes the third figure is always 1. [m.n.1]Propellanes may have a great variation in m and n but they will always contain at least one cyclopropane ring.

Penultimately, although this chapter is expected to contain serious subject matter, we shall not hesitate to specify certain examples, not because they are necessarily the most serious examples which may be fished out of the above-mentioned sources[1–3] but rather because they are the more piquant. Editors, much more often than not, frown upon such frivolous behavior, nay, e'en at seeing in the typescript the *mention* (God help us) of a light-hearted, perhaps (considered by some) humorous statement. My position is more tenable herein, rather than more tenuous. This is a book, not a journal; and the editor is a Mensch.

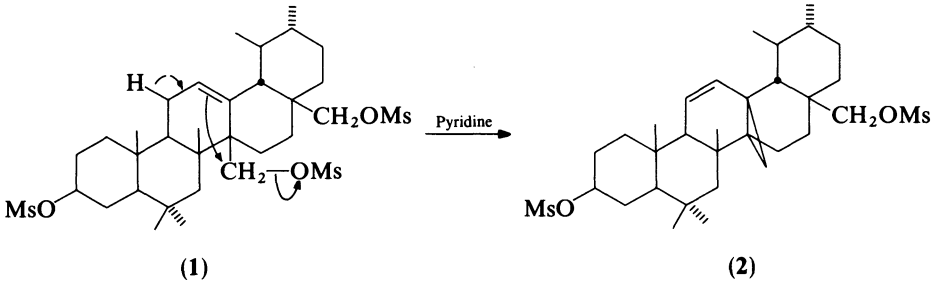
Finally I must address a word to any unthinking reviewer of my chapter. Mr (or Ms) Reviewer: please be advised that I have tried, certainly *without* full success, to cite all references extant to [m.n.1]propellanes in Refs 1–3 of this chapter. I have failed insofar as certain references have assuredly been unavailable to me; I didn't find them all. Thus, should you wish to appear scholarly in your review by comparing this chapter with material in Refs 1–3, say what you will but please do not accuse me of plagiarism. Of course I did not conduct a new literature search for the purposes of this chapter. I have merely selected citations I already had in Refs 1–3 and have organized the material in accord with the table of contents herein.

II. PREPARATION OF [m.n.1]PROPELLANES

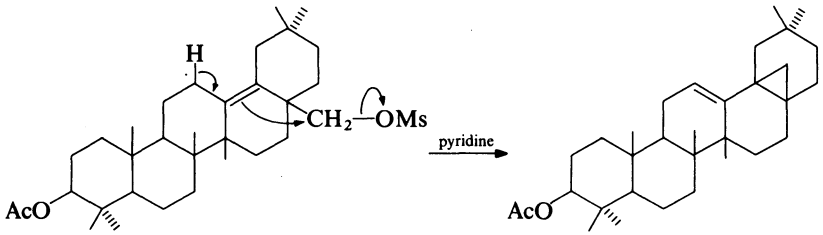
A. Solvolysis of Olefinic Substances containing Properly Disposed Leaving Groups

In the early days the most direct method for the preparation of [m.n.1]propellanes was not yet known. Therefore the early methods involved solvolysis of suitable substrates. The first cases appear to be the preparation of derivatives of [4.4.1]propellanes (i.e. m = n = 4) from a compound containing a good leaving group and a suitably situated double bond. Thus the triterpene derivative (**1**) was used which gave a [4.4.1]propellane involving rings C and D of the educt **2**[4].

Rings D and E in the triterpene derivative **3** may also be involved in the [4.4.1]propellane moiety of **4**[5].

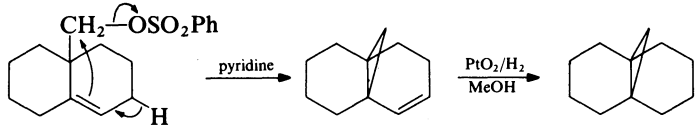


(1) (2)



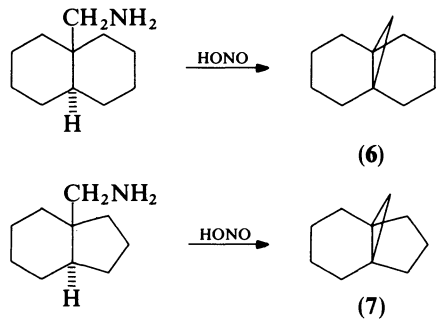
(3) (4)

The same authors showed that the same reaction, in principle, may give an unsaturated propellane, i.e. [4.4.1]propell-2-ene (**5**) whose reduction constituted the first synthesis of [4.4.1]propellane (**6**) itself[5].



(5) (6)

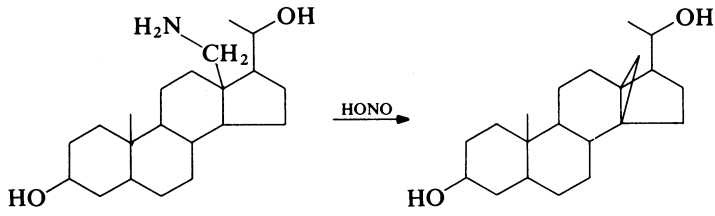
Other reaction conditions could also be used. Both [4.4.1] and [4.3.1]propellane (**7**) were prepared from suitable chosen amines with nitrous acid[6].



(6)

(7)

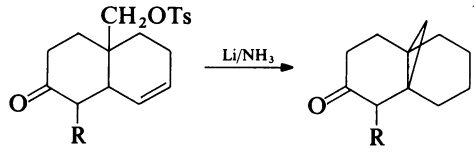
This approach was not limited to the bicyclic substrates and was applied also to steroid derivatives (e.g. **8**)[6].



(8)

B. Hydrogenolysis of Olefinic Substances containing Properly Disposed Leaving Groups

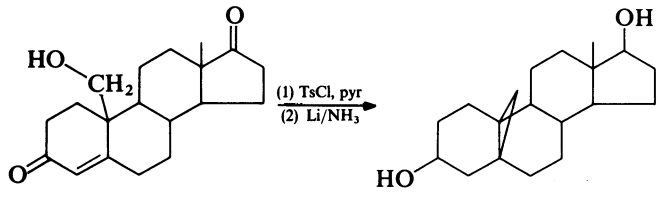
Reductive conditions rather than solvolytic ones could also lead to the [4.4.1] system; this time however, in contradistinction to the olefinic substrates studied by the ETH group[4,5] the double bonds are adjacent to a ketone function (cf. **9**)[7].



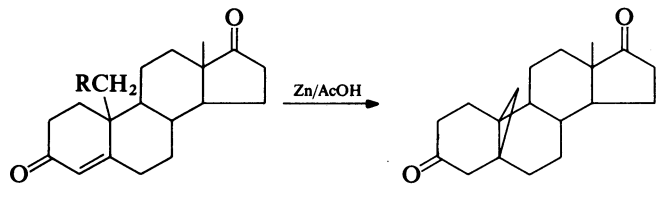
(9)

R = H, Me

Other examples for the use of reductive conditions employ the steroid substrates **10** and **11**[8,9].



(10)



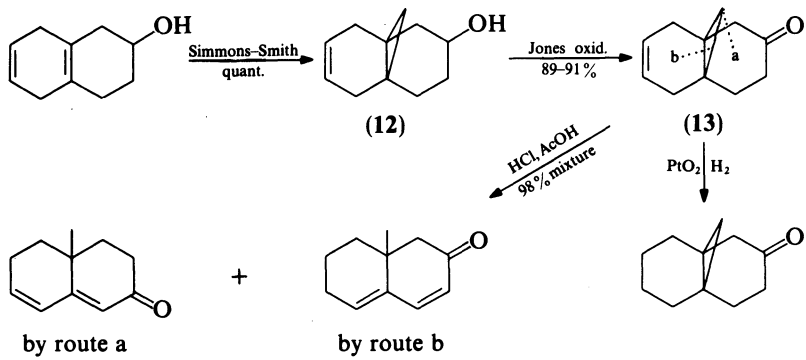
(11)

R = I, OTs

The only thing wrong with these steroids is fitting in, in print, an angular substituent at C(10). (Bicyclic systems do not present such a problem even when the angular substituent is relatively large! See below[12,13].)

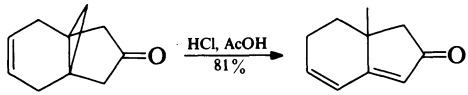
C. Carbene or Carbenoid Addition to Olefins

Sims, like many others, prepared propellanes with the view of destroying them; his motivation was to prepare an angular methyl group[10]. This is the first case we cite in which a carbenoid reagent generated from $Zn–Cu/CH_2Cl_2$ (Simmons–Smith reagent) was used to prepare the [4.4.1]propellenol intermediate **12**. The corresponding ketone (**13**) was prepared. As may be seen in Scheme 1, the cyclopropane ring was not destroyed by



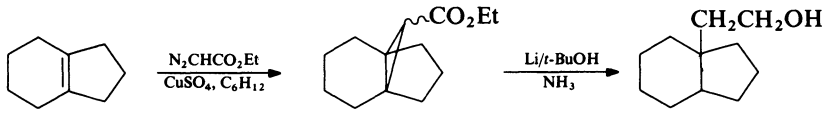
SCHEME 1

hydrogenolysis. Rather, acid did the job. The more symmetrical substrate by route b affords one angularly substituted product (**15**) in high yield[11].



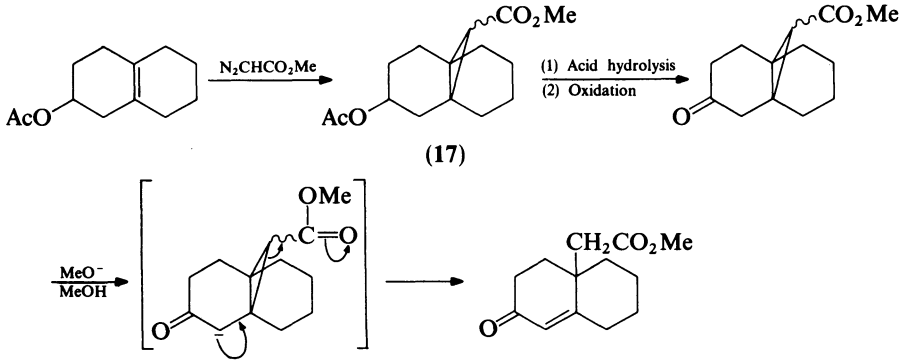
(**14**) (**15**)

House has similarly prepared an ester substituted [4.3.1]propellane (**16**) by employing ethyl diazoacetate as a carbenoid source, then hydrogenated the cyclopropane ring[12]. In view of his motivation the formation of a mixture of epimeric esters does not matter.



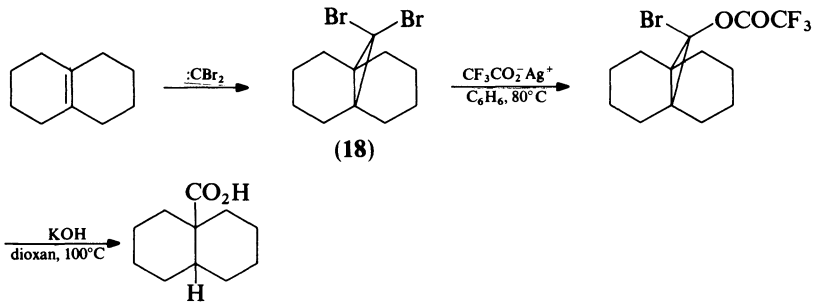
(**16**)

Another case where a (larger) substituted methyl group easily occupies, in print (and otherwise), the angular position in a bicyclic system (**17**) was similarly prepared but the cyclopropane ring was disrupted by employing basic conditions (Scheme 2)[13].

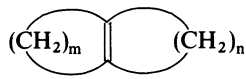


SCHEME 2

An angular carboxyl group has also been introduced via the intermediacy of the halogenated [4.4.1]propellane **18**. Here too the propellane was prepared by using a carbene[14].



Of course, carbenes have become the reagents of choice for preparation of [m.n.1]propellanes. They require the bicyclic olefin **19**, in which m and n may be either equal or unequal.



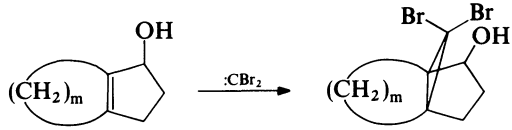
(19)

We shall discuss separately below the work of Vogel on the one hand and of Warner on the other, but before we do so let us cite several more examples of the synthesis and uses, for one reason or another, of [m.n.1]propellanes.

[4.4.1]Propellane upon hydrogenolysis with Pt/AcOH gives almost equal amounts of the *cis*- and *trans*-angular methyldecalins[15].

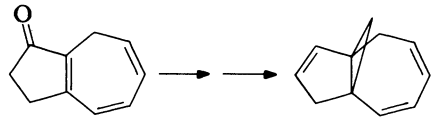
This result has been confirmed and extended for a number of Pt and Pd catalysts but [4.3.1]propellane gives a product mixture of 95% of the *cis*-angular methylhydrindan and only 5% of the *trans* isomer[16].

A series of [m.3.1]propellanols (**21**, m = 16, 13, 12, 5) have been prepared from the corresponding bicyclic allylic alcohols **20**[17]. These were used for the preparation of metacyclophanes.



(20) **(21)**

1,5-Methano[10]annulene has been prepared through the intermediacy of several [5.3.1]propellanes. The first of these, [5.3.1]propella-2,4,7-triene **23** was prepared by carbene addition to the trienone (**22**)[18]. It is capable of undergoing [2 + 2], [4 + 2] and [6 + 2] cycloaddition[19].

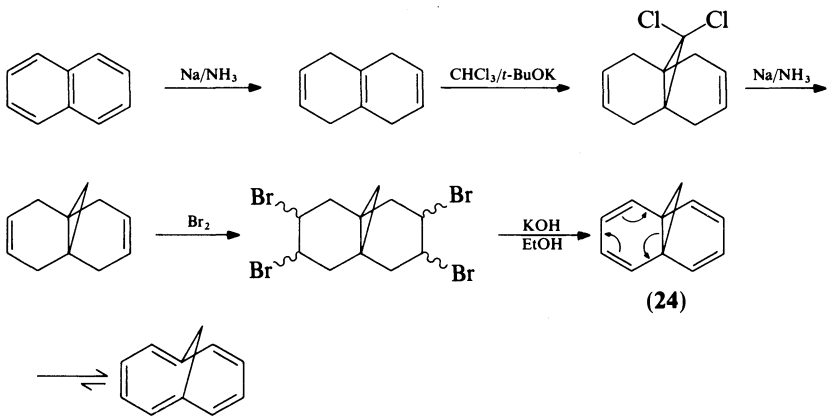


(23)

III. THE [4.4.1]PROPELLATETRAENE ⇌ 1,6-METHANO[10]ANNULENE EQUILIBRIUM

A. Attempted Synthesis of[4.4.1]Propella-2,4,7,9-tetraene and its Higher Homologs

A whole new field was opened when Vogel tried to synthesize [4.4.1]propella-2,4,7,9-tetraene (**24**) (alas, this name did not even exist at that time) in order to study the norcaradiene ⇌ cycloheptatriene equilibrium in this potentially new bis norcaradiene[20]. He was to find that none of the propellane is obtained. The 'open' fluxional isomer **25** is



(24)

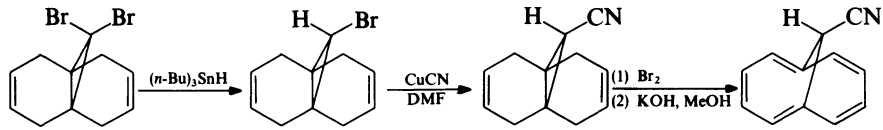
(25)

obtained exclusively, the conjoining bond knowing by its innate intelligence that by not standing on its position, aromatic gain may be reaped. The Vogel synthesis began with an aromatic compound and ended with another.

This was the beginning of a 'they lived happily ever after' story, for this observation was followed by a goldmine of beautiful chemistry.

It turns out that the [4.4.1]propellatetraene structure may be stabilized by proper (di) substitution at C (11). Thus the 11-methyl-11-cyano-, the 11,11-dicyano- (albeit unstable, rearranging to the dicyano-substituted benzocycloheptadiene), and the 11-benzyl-11-cyano-derivatives exist in the propellane form[21].

Yet monosubstitution at C (11) does not suffice and the product is the 'open' bridged annulene, e.g. **27**. Its preparation illustrates many other cases in which [4.4.1]propellane intermediates are formed and exist as propellanes at lower oxidation states (cf. **26**). But once the tetraenic one is arrived at, the product more often than not prefers to exist as the more stable aromatic bridged annulene.



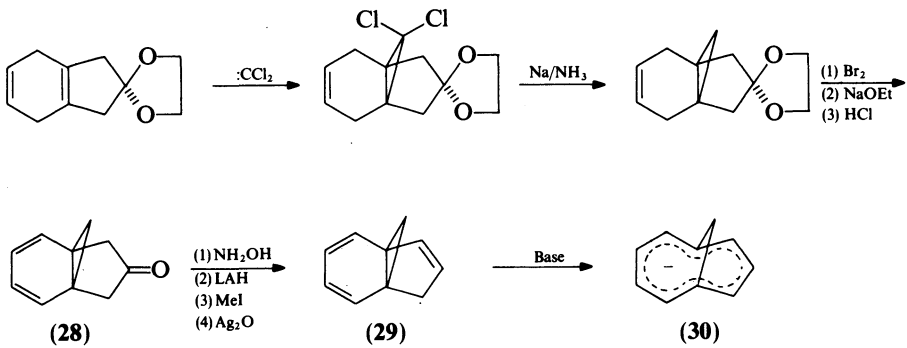
(26) **(27)**

It should perhaps be noted that though this point is not discussed by the authors, exchange of Br for CN in the foregoing reaction scheme presumably does not occur via an S_N2 process (see Section V).

B. Preparation of Other [m.n.1]Propellanes

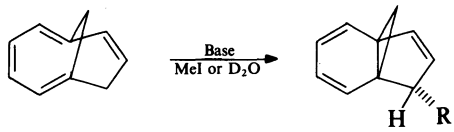
Many other tricyclic compounds embracing two as the norcaradiene system can be stable in the 'closed' propellane form; certainly when the oxidation state is still lower, the propellane form does not 'open'.

Thus the [4.3.1]propelladienone **28** has been prepared[23]. The [4.3.1]propellatriene **29** derived therefrom upon treatment with base gives, however, the bridged cyclono-



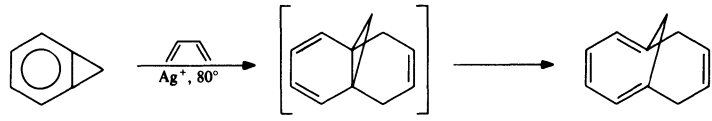
(28) **(29)** **(30)**

natetraenyl anion **30**[23] which may be stereospecifically methylated or deuteriated to **31**, R = Me or D[11, 24].



(31)

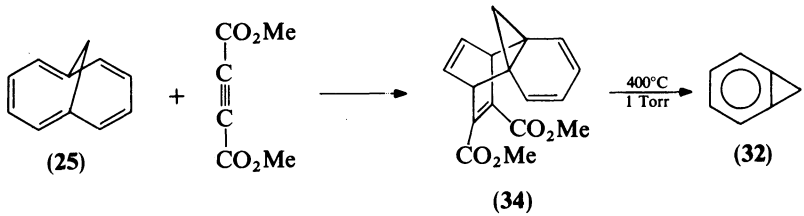
Yet another case where a bridged compound (33) is obtained rather than the propellane was found when benzocyclopropene (32) reacted with butadiene in a silver-catalyzed reaction[25]. This is a case where the sextet of electrons suffices for stabilizing the open



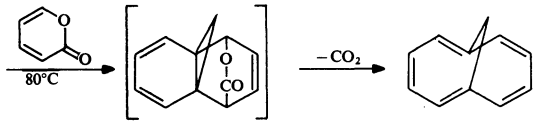
(32) (33)

norcaradiene structure. We have no clear-cut rule to go by in predicting the direction of the norcaradiene–cycloheptatriene equilibrium.

A piquant reaction is that of benzocyclopropene (32) which is formed via a retro-Diels–Alder reaction of the adduct of 1,6-methano[10]annulene with acetylenedicarboxylic ester (34). This adduct is fragmented at 400° C and 1 Torr. Reaction of the retro-product with another dienophile gives the unstable adduct 35 which spontaneously loses CO_2 to afford . . . 1,6-methano[10]annulene (25)[26] La Ronde!

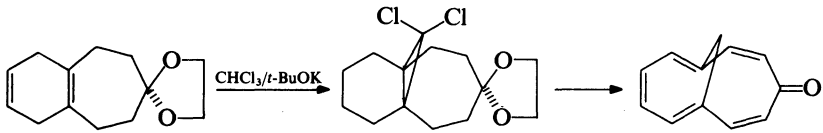


(25) (34) (32)



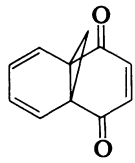
(35) (25)

The 10 π-electron analog of tropone (38) has been prepared[27]. The addition of dichlorocarbene to 36 gives the [5.4.1]propellane derivative (37) which was converted in several steps into the desired compound.



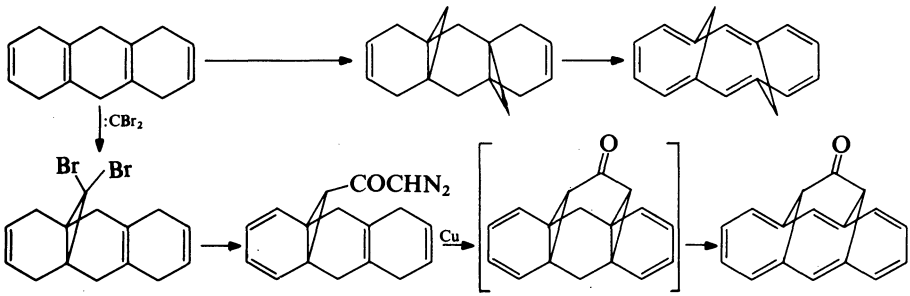
(36) (37) (38)

The interesting [4.4.1]propelladiene–enedione **39** has been prepared[28]. It contains a diene and a dienophile in the same molecule and it indeed dimerizes[29].



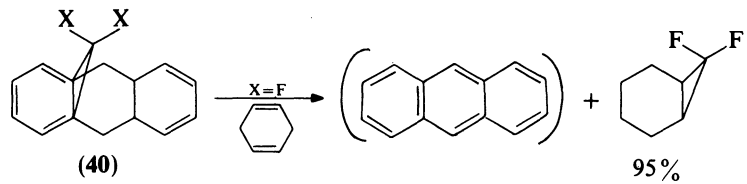
(39)

Many propellane intermediates have been used in the synthesis of various di-bridged[14]annulenes, such as those shown in Scheme 3[30,31].

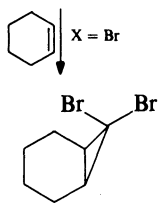


SCHEME 3

11,11-Dihalo-1,6-methano[10]annulenes **40** have been used as dihalocarbene transfer agents[32].



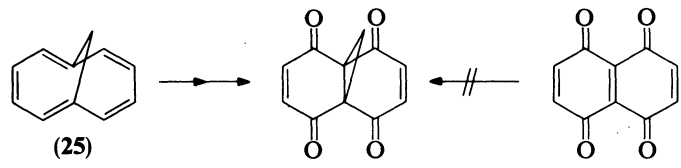
(40)



'high yield'

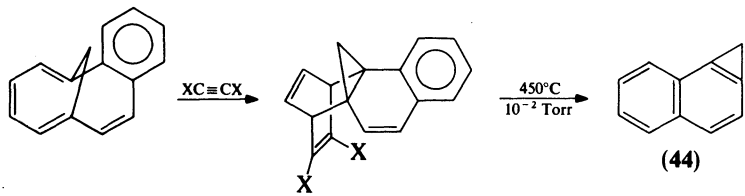
X = F, Cl, Br

The homodiquinone **42** was prepared in several steps from 1,6-methano[10]annulene[33]. It could not be obtained by direct attack of the tetrasubstituted double bond of naphtho-1,4,5,8-diquinone (**41**).



(**25**) (**42**) (**41**)

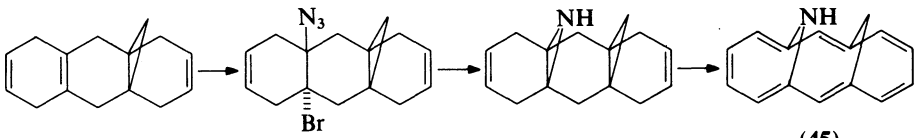
1*H*-Cyclopropa[a]naphthalene (**44**), was prepared via the [4.4.1] propellane intermediate **43**[3].



(**44**)

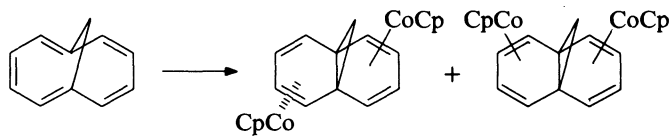
X = CN, CO_2Me (**43**)

[4.4.1]Propellanes are intermediates in the synthesis of *syn*-1,6-imino-8,13-methano[14]annulene (**45**)[35].



(**45**)

1,6-Methano[10]annulene gives with $CpCo(C_2H_4)_2$ two complexes (**46** and **47**) of the [4.4.1]propellatetraene[36].

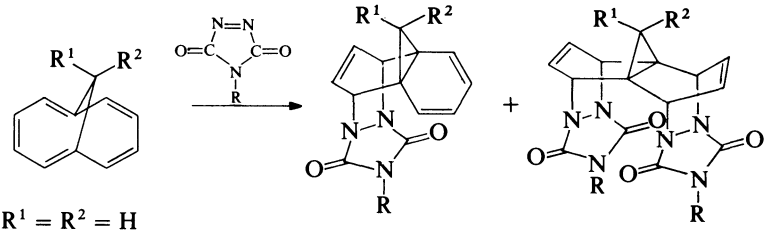


(**25**) (**46**, 35%) (**47**, < 1%)

Within the framework of reactions of various propellane substrates with very reactive dienophiles, *N*-methyl- and *N*-phenyl-triazolinediones, 1,6-methano[10]annulene itself and many bridge- and ring-substituted derivatives were subjected to such Diels–Alder reactions. All of the products are (more complex) [4.4.1]propellane derivatives. In general it is clear that the rates of reaction are very much slower than those of various tetraenic,

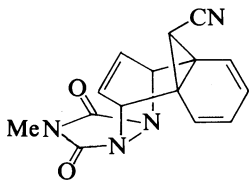
trienic, and dienic propellanes. This is understandable, for in analogy to virgins long before our permissive era, the substrates do not want to give up their aromaticity.

Whilst these red dienophiles attack a large variety of [4.4.2], [4.4.3] and [4.3.3]propellanes[1-3], instantaneously, the red color disappearing as in a titration, the color disappears in hours or in days with various 1,6-methano[10]annulenes[37]. Examples follow:

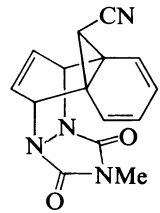


$R^1 = R^2 = H$
$R^1 = H$; R^2 = CN, Br, OAc, OH, CO_2H
R = Me, Ph

For the first time in our work we were able to isolate in the case of 11-cyano-1,6-methano[10]annulene a roughly 1:1 mixture of the *anti-endo*-adduct **48** and *anti-exo*-adduct **49** whose structures and configurations were determined by X-ray crystallography[38].



(**48**, *anti-endo*)

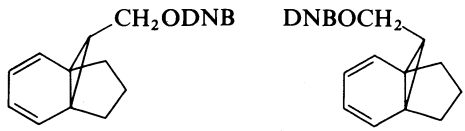


(**49**, *anti-exo*)

IV. SOLVOLYSIS OF [m.n.1]PROPELLANE DERIVATIVES

In rereading the various papers on this subject it seems that little significance is to be attached to the results and little insight to be gained from them.

Thus the rates of solvolysis of various 3,5-dinitrobenzoates (ODNB) of 11-hydroxymethyl derivatives of [4.4.1]propellanes of different oxidation states all fall within a factor of 10[39]. The same holds for various epimers of the same derivatives of 10-hydroxymethyl-(also on the bridge) derivatives of various [4.3.1]propellanes of different oxidation states. The rate difference between the extremes (**50** and **51**) was 80[40]. The authors attribute the difference to 'conjugative factors'.



(50) rel. rate 80.2

(51) 1.00

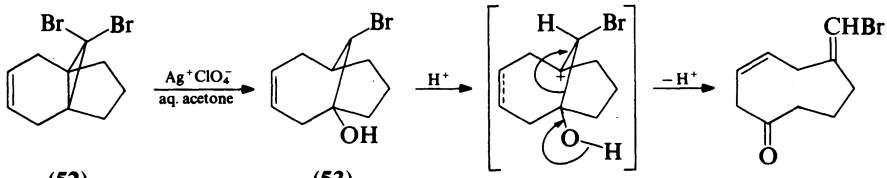
Work has also been done on solvolysis of *syn*-8-tosylates in the [4.3.1] system (*syn*-with respect to the cyclopropane ring)[41], and in epimeric, *syn*- and *anti*-7-*p*-nitrobenzoates of [4.3.1]propellane and in *syn*- and *anti*-6-*p*-nitrobenzoates of [3.3.1]propellane[42].

Solvolysis of a series of benzo[4.3.1]propellane *p*-nitrobenzoates substituted in the aromatic ring is interpreted in terms of a homonaphthalenium cation[43,44].

A. Silver Ion Assisted Solvolysis

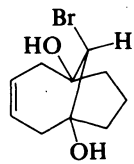
This is mainly the work of Philip Warner who also (cf. Ref. 44) appears to have been introduced into the field of propellanes by Saul Winstein in work concerned with the protonation of 1,6-methano[10]annulene, work in which they ruled out the presence of a propellane-type cation[45].

It was shown that silver ion promotes solvolysis of several (saturated and unsaturated) 11,11-dibromopropellanes as exemplified in the accompanying scheme[46]. The fragmentation method invokes an 'anti-Bredt' intermediate.



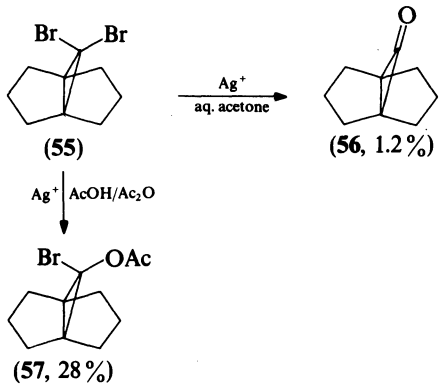
(52) (53) major product

It was later found that the bicyclic diol **54**, accompanies the above bromoketones[47]. Similar reaction sequence takes place with the saturated analogs[47].



(54)

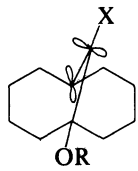
In a silver ion assisted solvolysis of the dibromo[3.3.1]propellane **55** in acetone, a mixture is obtained with a surprising product (**56**) albeit only in 1.2% yield, accompanying



three bicyclic products[48]. However, in acetic acid, the tricyclic bromoacetate **57** was the major product!

The mechanism of such solvolysis of 11,11-dihalo[4.4.1]propellanes leading to bridgehead olefin formation has been discussed in the light of various alternatives[49].

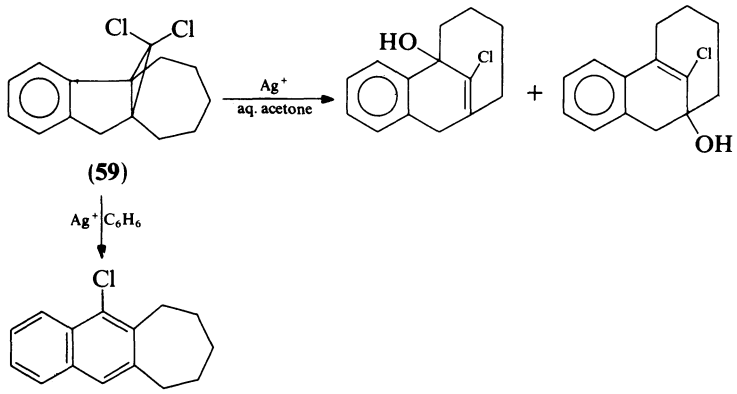
The latter substrates were deuteriated and mass spectral fragmentation of the products of solvolysis was studied[50]. The authors concluded that both unassisted and Ag^+-assisted solvolysis were stereoretentive and that the intermediate cations and the bridgehead olefins do not interconvert. They believe that a perpendicular cation, **58**, does not intervene but the precise structure of the intermediates is still uncertain.



(58)

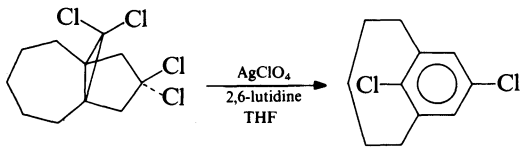
Finally in this connection, two examples are cited in which silver ion causes rearrangement of 11,11-dihalopropellanes to '*meta*' bridged compounds[51,52].

The benzo-substituted [5.3.1]propellane (**59**) when solvolyzed in aqueous acetone gives the mixture shown, but in dry benzene a linear tricyclic product results[51].



(59)

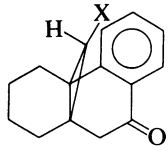
In the second instance, a *meta*-bridged-dichlorobenzene derivative (**61**) was prepared by rearrangement of the [5.3.1]propellane **60**[52].



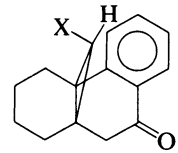
(60) **(61)**

V. S_N2-REACTION IN A CYCLOPROPANE RING? [m.n.1]PROPELLANES AS MODELS

A report on nucleophilic substitution at a cyclopropyl carbon atom, with retention of configuration (i.e. **61**, X = Br → **61**, X = OAc; **62**, X = Br → **62**, X = OAc) caused excitement or consternation when it appeared[53].



(*syn*-**61**, X = Br, solid; X = OAc, oil)

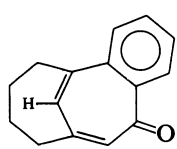


(*anti*-**62**, X = Br, solid; X = OAc, solid)

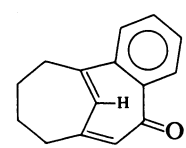
The paper discussed possible mechanisms for nucleophilic substitution at a cyclopropane carbon with particular attention to retentive replacements. From the NMR spectra of the *syn*- and *anti*-bromides and acetates shown above, it was concluded that smooth stereospecific substitution of bromide by acetate had taken place under typical S_N2-type conditions. For the *anti*-pair, comprising two solids (one member of the *syn* pair is an oil), this conclusion was confirmed by X-ray structure determination of both educt and product.

Of course, inversion is the expected course of a kinetically controlled S_N2 reaction at a saturated carbon. The same bromide substrates were again converted into the respective acetates with the same reagent as used before—tetramethylammonium acetate in acetone[54]. Kinetic control was ascertained through the fact that each epimer gave a stereoisomeric product. Further, retention of configuration was established by the X-ray structures. The reactions were facile, with high yields at room temperature, although one might expect a very slow reaction at a cyclopropyl carbon even under stringent conditions.

The authors[54] therefore considered the possibility that these transformations do not result from direct substitution but, rather, that elimination of HBr occurs, with subsequent addition of acetic acid. Acetate ion could abstract a proton from the carbon α- to the carbonyl group, with breakage of the propellane conjoining bond, ejecting bromide ion, and introducing a double bond with (*Z*)-configuration (cf. **63**) for the *syn*-substrate. Whatever factors conserve stereospecificity in this isomer to give a (*Z*)-olefin, would operate in the stereoisomeric *anti*-bromide to give an (*E*)-olefin, **64**. Both would be highly strained, would react with acetate ion from the same side of the single-carbon bridge with subsequent ring-closure and protonation to re-form the cyclopropane ring. The mechanism is not of the S_N2 type but could follow second order kinetics and would explain the retentive nature of the reaction. The authors cite as 'a remote analogy' the Ag^+-assisted hydrolysis of 11,11-dibromo[4.3.1]propellane[46,47].



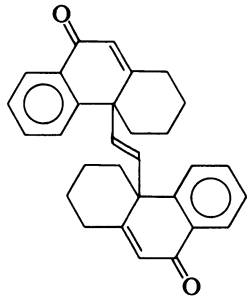
((*Z*)-**63**)



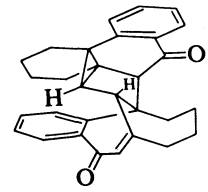
((*E*)-**64**)

Finally, reaction of the *syn*- and *anti*-bromides at high concentration with acetate ion in aprotic polar solvents permitted the obtention of evidence for this elimination–addition

mechanism[55a]. In addition to the acetates described above, dimeric dehydrohalogenation products were formed. Their isolation may be explained through the intermediacy of the (*Z*)- and (*E*)- benzotropones **63** and **64**.



(65)

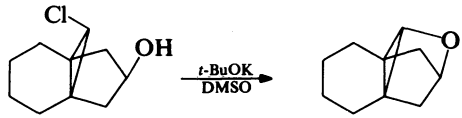


(66)

The *syn*-bromide gave the *syn*-acetate along with the dimers **65** and **66**. Dimer **65** is formally one of a carbene; **66** is a [3 + 2]cyclodimer formed from the *syn*-but not from the *anti*-bromide. Further details are found in Liesner's thesis[55b].

This is a truly fascinating story which again emphasizes, perhaps unnecessarily, the intelligence of molecules. Rather than undergo an S_N2 reaction at a cyclopropyl carbon, they find extraordinary ways to avoid this. Sometimes they jest with the mere mortals dealing with them but in this case they were ultimately found out.

A case of a direct S_N2 process which is intramolecular and which is reported to occur with inversion is the conversion of **67** to **68**[55c]. It is clear that the authors are aware of the problem but they exclude other mechanisms.



(67) **(68)**

Since mono-adducts obtained from reacting 11-substituted bridge[10]annulenes with triazolinediones contain a substituted cyclopropane ring, we attempted nucleophilic displacement under stringent reaction conditions. Even with 'naked' fluoride ion the substrates were recovered unchanged[37b].

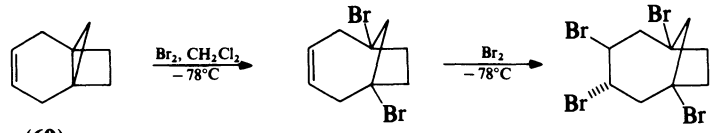
VI. SMALL-RING [m.n.1]PROPELLANES

Although it is not surprising that Wiberg extended to tricyclic systems (propellanes) his studies on hybridization of the bridgehead carbons in small-ring bicyclic compounds and the chemistry resulting therefrom, we shall perhaps extend somewhat the realm of the propellane substrates. This is done pragmatically (every definition is, by definition, arbitrary) in order to permit inclusion of certain piquant results.

Let us begin with one of these.

Every teacher of the first course of organic chemistry, towards its beginning, emphasizes the different behavior of saturated and olefinic hydrocarbons towards halogens. The influence of ring strain is discussed rather later in the course. And a good thing too, for

what would the poor beginner gain from too early an introduction to the bromination of [4.2.1]propell-3-ene (**69**)[60]?

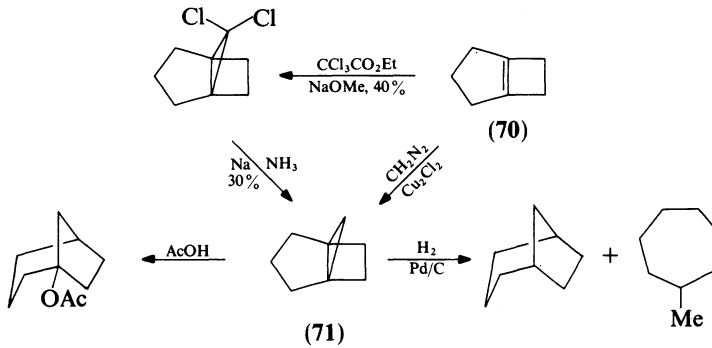


(**69**)

Clearly this reaction allows us to define small-ring propellanes in such a way as to include m = 4. May m and n both be 4? Certainly not, on the basis of the refusal of the conjoining bond in a [4.4.1]propellane to add halogens or other reagents. Thus, by a pragmatic approach based on knowledge of the behavior of these substances, we allow $m + n \leqslant 6$ for [m.n.1]propellanes, i.e. $m + n + 1 \leqslant 7$. More generally, small-ring propellanes are so defined as to allow their indices to be equal or smaller than 8. (This does not clash with various oxidation states in, say, [4.4.1]propellane in which the conjoining bond electrons prefer to participate in the π-system of the [10]annulene or a sextet within the cyclodecane ring, see Section III). Such a definition allows us to include [4.2.2]propellane which certainly belongs within the group. The weakness of such an (arbitrary) definition lies in the fact that [4.3.1]propellane, for example, is not really a member of this exclusive community. But let us not worry too much about this point and continue our discussion of small-ring propellanes within the confines of our present day knowledge and understanding. We shall see that we do not yet understand the niceties of a subject which, perhaps with insufficient reverence, may be formulated as 'when is a bond a bond'? or 'when is (or is not) a propellane a propellane?'.

But before we turn to this aspect of the structure of not only [1.1.1]propellane but certainly of other [m.n.1]propellanes, let us consider how these and other small-ring [m.n.1]propellanes are prepared, in more or less chronological order.

Wiberg and Gassman have independently prepared [3.2.1]propellane (**71**) as shown in the accompanying scheme. Wiberg added dichlorocarbene to bicyclo[3.2.0]hept-1(4)-ene (**70**)[56,57a] whilst Gassman added carbene itself to the same substrate[58]. The half-life of [3.2.1]propellane is 20 hours at 195°C[57]. Acetic acid adds rapidly within less than 5 min to the conjoining bond and affords the bridgehead acetate[57a].



(**70**)

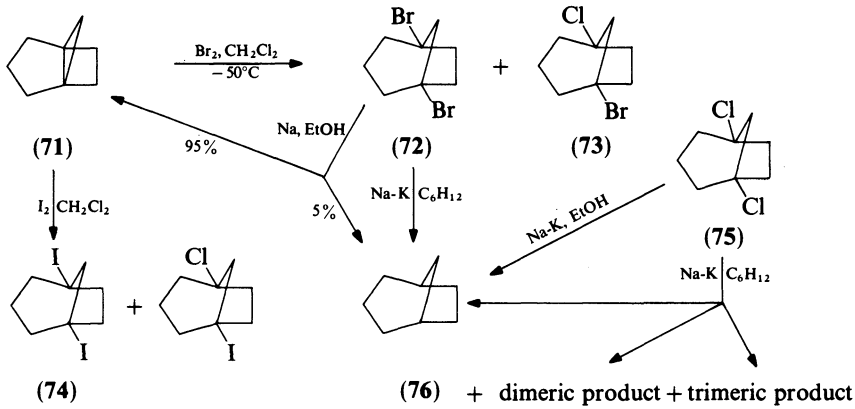
(**71**)

Its thermal stability was explained by invoking the forbidden concerted thermal fragmentation of a cyclobutane ring. In such a rigid molecule even stepwise cleavage beginning with the conjoining bond would closely resemble a concerted process. Nor is a

biradical at the central bond followed by hydrogen migration, as in cyclopropanes, reasonable as this would violate Bredt's rule, which though no longer sacrosanct ought still to hold for this system Cleavage of the cyclopropane bonds is also not favored since it must needs be followed by an alkyl shift, a process uncommon in free radical reactions.

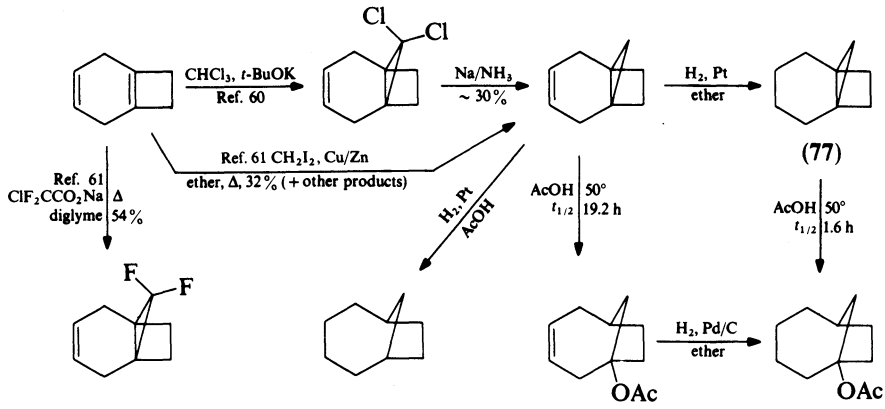
Its heat of combustion could't be measured because it is readily oxidized by oxygen to give a polymer.

In the full paper on [3.2.1]propellane several additional results were reported[57b]. Bromination in CH_2Cl_2 at $-50°C$ afforded not only the dibromide **72**. This was accompanied by a chloro–bromo derivative (**73**) indicating that a bromo–bridgehead radical or cation intermediate then either reacts with bromine or abstracts chlorine from the solvent. The Wiberg group also reported a new approach, from the bridgehead dibromide to the parent propellane as shown in the accompanying scheme.



The reverse reaction from the dibromide to the propellane parent had already been reported by electrochemical means[57c]. The diiodide **74** gives [3.2.1]propellane with *t*-BuLi at $-77°C$[57d]. Reduction of **72** and the dichloride **75** give **76**. The length of the conjoining bond in 8,8-dichloro[3.2.1]propellane is 1.572 Å[57e]. Its minimum strain energy was estimated to be 60 kcal mol^{-1} [59].

[4.2.1]Propellane (**77**) was similarly prepared[60].



We have already alluded above[60,61] to addition of bromine to [4.2.1]propell-3-ene. The saturated hydrocarbon also adds bromine to the conjoining bond at −78°C, a reaction analogous to that of acetic acid addition. The same [4.2.1]olefin is hydrogenolyzed across the conjoining bond if platinum is used in acetic acid; in ether the [4.2.1]propellane survives.

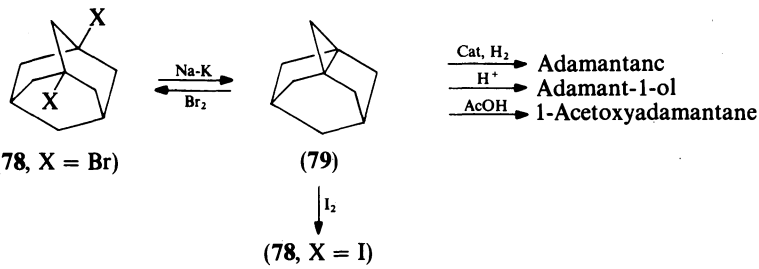
The much slower addition of acetic acid[60] to the [4.2.1]propellane and -ene as compared to that to [3.2.1]propellane[51a] is, of course, attributable to their relative strain. The rate differences between the olefinic ($t_{1/2}$ = 19.2 h at 50°C with AcOH) and saturated ($t_{1/2}$ = 1.6 h) [4.2.1]substrates are perhaps not so large to worry about excessively.

The regiospecificity of attack by triazolinediones in a series of [4.n.1]propelladienes, is always *anti* to the cyclopropane ring[62].

[3.3.1]Propellane was also studied from the viewpoint of ring strain[63]. The compound was thermally stable to heating at 180°C for 22 h, was not sensitive to oxygen and was not hydrogenolyzed using Pd/C for 6 h under a hydrogen pressure of 3 atm in ethanol. It is, however, very reactive towards bromine or acetic acid addition to the conjoining bond. It is less reactive than [4.2.1]propellane or dehydroadamantanes (which contain a [3.3.1]propellane moiety, see below), and is calculated to have ca. 46 kcal mol^{-1} ring strain.

A [3.3.1]propellane moiety is responsible for the reactivity of 1,3-dehydroadamantanes[64]. The two bridgehead carbons involved exhibit the inverted tetrahedral geometry[65] as originally defined by Wiberg for small-ring-propellanes[57b,66a]. The length of the conjoining bond in the corresponding cyano derivative of 1,3-dehydroadamantane, 1-cyano-tetracyclo[3.3.1.1^{3,7}. 0^{3,7}]decane, is 1.647 Å. The enthalpies of acetolysis of the conjoining bonds in 1,3-dehydroadamantane and in [3.2.1]propellane have been determined. From these values, calculated strain energies of 64 and 67 kcal mol^{-1}, respectively, were obtained[66b].

1,3-Dehydroadamantane (**79**) is formed from 1,3-dibromoadamantane, (**78**, X = Br).

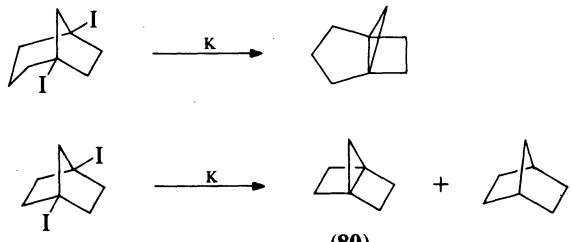


(**78**, X = Br) (**79**) (**78**, X = I)

Kogay has added many other, somewhat more complicated reagents to the conjoining bond, e.g. diethyl malonate, *p*-toluenesulfonamide, and aniline[67a] benzenesulfonyl chloride and *p*-tosyl chloride[67b]; pyridine and iodine afford addition of iodine and a pyridinium iodide group to the bond[67c], mercuric acetate in ethanol in the presence of chloride ion affords addition of HgCl and an ethoxy group[67d]. A recent review includes a discussion of the reactions of 1,3-dehydroadamantane[68].

A new technique (applicable also for [3.2.1]propellane (**71**), cf. Ref. 57) has been developed using gas phase dehalogenation of the bridgehead diiodide with alkali metal vapor and leading to the corresponding propellane. This is then followed by trapping in an inert gas matrix (Ar). The heretofore unknown [2.2.1]propellane (**80**) was prepared, accompanied by norbornane[69]. The potassium vapor is diluted with a sonicated stream of nitrogen.

Electrolytic reduction of 1,4-dihalonorbornanes (**81**) at mercury electrodes in DMF provided evidence for the intermediacy of [2.2.1]propellane[70]. Anomalously long-range

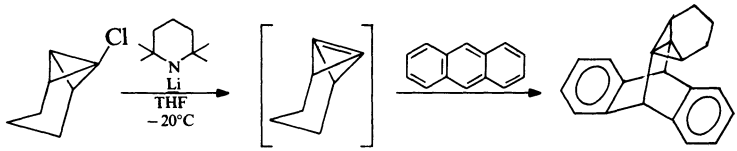


(80)

halogen hyperfine splitting in 4-halo-l-norbornyl radicals (**82**) has been interpreted in terms of a direct through-space interaction, as shown, involving a [2.2.1]propellane hybrid (**83**)[71].

(**81**, X = Y = I; X = Br, Y = I) (**82**, X = Br, I) (**83**)

The compound **85** containing a [4.1.1]propellane moiety was first obtained by a husband and wife team through trapping the strained intermediate **84** with anthracene[72a].

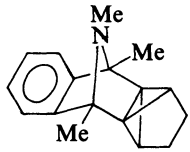


(**84**) (**85**)

A lower homolog also containing a [4.1.1]propellane moiety was also prepared and its X-ray structure determined. The bicyclobutane portion in this case was bridged by a two-carbon chain rather than the three carbon chain shown above [72b,c] (cf. Ref. 72f–i for the synthesis of additional examples).

The structure of a [4.2.1]propellane derivative prepared in 35–45 % yield similarly to the [4.1.1]homolog from 1-chloroquadricyclane in the presence of anthracene was also determined, again exhibiting the 'inverted tetrahedron' phenomenon[72d].

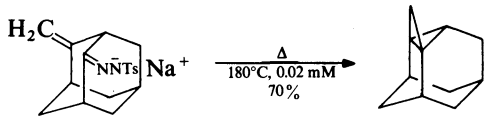
It was in connection with the results obtained for electron density distribution in the aza[3.1.1]propellane **86**[72e] that the question 'when is a propellane a propellane?' could be posed. The length of the conjoining bond (the basis for the definition of propellanes:



(**86**)

propellanes are tricyclic systems conjoined in a common carbon–carbon bond!) is 1.574 Å. But electron density difference maps at 96 K show that there is no significant deformation density along the line of the conjoining bond, either between the atoms or outside them, i.e. the total charge density along this line is closely similar to the sum of the densities from the isolated spherical atoms. This result albeit gratifying to the theoreticians who made LCAO calculations for [1.1.1]propellane a decade earlier[73] still presents a paradox in view of the importance of the conjoining bond in propellane chemistry. This point will be discussed below but does not appear to have been either understood or explained in a satisfactory way.

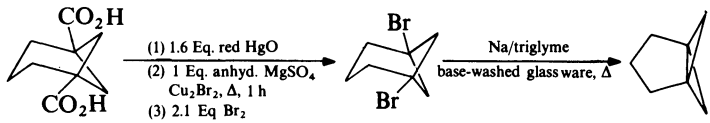
Another husband–wife team (cf. Ref. 72a) has prepared 2,4-methano-2,4-dehydroadamantane which contains a [3.1.1]propellane moiety (**88**) by intramolecular cycloaddition, of **87**[74a]. (One may muse about what it is that attracts such teams to small-ring propellanes. Imagine what great progress there might have been had Mrs Wiberg entered this field!) ^{13}C-chemical shifts of the inverted carbons was discussed[74b] (cf. Ref. 74c).



(**87**) (**88**)

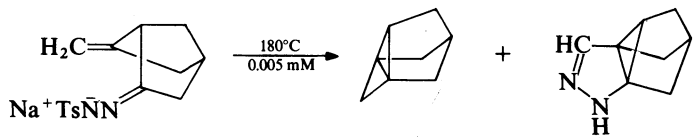
Methanol, acetic acid, and HCl cleave the bicyclobutane system not necessarily by addition to the conjoining bond. Carbon tetrachloride, TsCl, and PhSH, however, behave in the catholic manner in this respect. The authors make the point that these results indicate high electron density at the back side of the inverted carbon atoms and a decrease of electron density between them.

An example of oneupmanship followed immediately. Gassman published the synthesis of [3.1.1]propellane (**89**) itself[75]. Though unstable when concentrated, it may be stored in solution. It was prepared as shown and ^{13}C-NMR data were provided.



(**89**)
isolated at −78°C

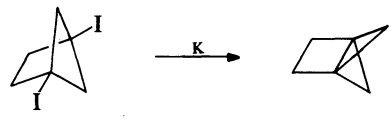
This challenge was met in Yugoslavia. 2,6-Methano-2,6-dehydronorbornane **91** the [3.1.1]propellane derivative (accompanied by the diaza [3.3.1]propellane shown) was prepared from **90** and studied[76]. It is said to be the most strained carbocyclic propellane to have been prepared. The compound is thermally unstable, decomposing completely within



(**90**) (**91**) (**92**)

30 min in C_6D_6. At -20 °C it reacts rapidly with oxygen and adds either CCl_4 or TsCl in chloroform instantaneously to the conjoining bond. It also readily adds HCl to this bond at -80°C. Be the above claim as it may, it is only fair to mention that it was made before the somewhat later appearance of Ref. 78.

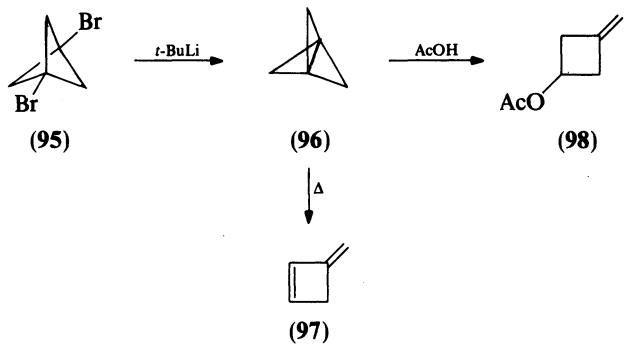
[2.1.1]Propellane (**94**) was synthesized from 1,4-diiodobicyclo[2:1.1]hexane (**93**) using potassium vapor and isolated in a nitrogen matrix[77]. It was tentatively identified on the basis of its infrared spectrum. The paper includes a table of infrared frequencies for



(**93**) (**94**)

strained small-ring propellanes. In contrast to [2.2.1]propellane which as usual adds bromine to the conjoining bond, the [2.1.1]homolog does not give an isolable analogous product. A variety of unidentified products, some of which were polybrominated, were obtained.

The ultimate in small-ring propellanes (C_2 exists but I don't consider it to be [0.0.0]propellane), [1.1.1]propellane (**96**), was finally synthesized from 2,3-dibromobicyclo[1.1.1]pentane (**95**) with *t*-BuLi[78]. It undergoes thermal rearrangement to **97** with a half-life of 5 min at 114°C. Thus, Wiberg's prediction that this compound ought to be relatively stable as compared to other small-ring propellanes is amply borne out. In acetic acid it affords 1-acetoxy-3-methylenecyclobutane (**98**).

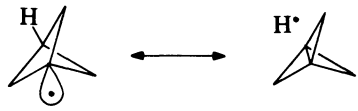


(**95**) (**96**) (**98**)

(**97**)

In this paper[78] the relative stabilities of various small-ring propellanes are discussed in terms of enthalpies of hydrogenolysis of the conjoining bond and dissociation energies of this bond in the various substrates. This is perhaps the place to state that the mechanism of addition of bromine, in the dark, to the conjoining bond of several [m.n.1]propellanes, has been discussed in general[79]. It is concluded that thermally initiated low temperature radical chain addition to the cyclopropane rings is involved.

A [1.1.1]propellane moiety (**100**) is believed to be involved as an important contributor in the valence bond resonance structure with the bridgehead bicyclo[1.1.1]pentan-1-yl radical **99**, which appears to have one of the largest γ-proton ESR hyperfine splitting constants for alkyl radicals known to man[80].



(99) (100)

We turn now to theoretical studies carried out on small-ring [m.n.l]propellanes (which often include other small-ring propellanes which do not contain a cyclopropane ring).

We have already mentioned the prophetic paper by Newton and Schulman on [1.1.1]propellane[73]. Assuming D_{3h} symmetry for the substance, they calculated lengths for the side bonds and the conjoining bond, of 1.53 Å and 1.60 Å, respectively. They calculated that the localized orbitals of the conjoining bond have a negative overlap population between the bridgehead carbons, indicating that they are directed away from each other. This implied a non-bonding or perhaps an antibonding interaction. Then, nine years later, the X-ray work of Dunitz *et al.* on a Szeimies [4.1.1]propellane with the 1,1-ears pinned down by a two-carbon clothespin, afforded full experimental justification for this prediction, albeit one of the rings involved in the propellane moiety is a cyclohexane rather than a cyclopropane[72e] (see above).

Strain in small-ring propellanes has been discussed in the light of strain relief afforded by rupture of their conjoining bonds[81a]. Bonding is not yet fully understood. A vibrational analysis has been undertaken in order to obtain more insight. These propellanes have an intense low frequency band, the frequency increasing as the ring size decreases, i.e. [3.2.1], 515 cm^{-1}; [2.2.1], 530 cm^{-1}; [2.1.1], 574 cm^{-1}, [1.1.1], 603 cm^{-1}. This is assigned to the antisymmetric combination of peripheral C–C bond stretches viewed as a 'bobbing' mode in which the two bridgehead carbons move up and down in unison with respect to the plane of the other carbon atoms, the hydrogens moving as a counterpoise. Optimized conjoining bond lengths of the propellanes were calculated by *ab initio* and MNDO methods. 'They are mostly strikingly normal, revealing little of the misery in which the molecules find themselves.' These nevertheless range from 1.631 (1.543) for [1.1.1], 1.596 (1.594) for [2.1.1], and 1.471 Å (1.534) for [2.2.1] [MNDO value (6-31G* or 4-31G value)], depending upon the calculation method.

A paper well worthwhile reading on this subject discusses the energies of optimized structures of various monocyclic, bicyclic and tricyclic propellane structures by the 4-31G and 6-31G* basis sets[81b], including [2.2.1], [2.1.1] and [1.1.1]propellanes which concern us here. Energies of hydrogenolysis of their conjoining bonds have been calculated and compared with experimental results. These become more negative in the order [1.1.1], [2.1.1], [2.2.1]. After the [2.2.1] had been obtained from its bicyclic bridgehead diiodide, the calculations suggested that the other small-ring propellanes could be similarly prepared, and with greater ease. This was confirmed experimentally (see above). The enthalpies of formation and strain energies of these compounds were estimated. The effect of polarization functions on their energies and structures was discussed and the electron density changes for the conjoining bonds were calculated. The paper ends with the following:

'Despite the lack of traditional bonding character for the central bond, our estimate of the difference in energy between the [1.1.1]propellane and a singlet diradical with the geometry of bicyclo[1.1.1]pentane suggests a large "bond dissociation energy"[81c]. How can one have a relatively strong "bond" without much bonding character? This question is being explored by calculating the energy changes in stretching the central bond in the propellane by using the GVB formalism, which allows correct dissociation, as well as by

both a theoretical and experimental study of the molecular vibrations of the [1.1.1]propellane. The results of these investigations will be reported at a later time.'

The Majerskis have commented on the nature of the conjoining bond in small-ring propellanes[74c].

A paper entitled 'Chemical bonds without bonding density' describes a new way of analyzing weak bonds, such as, *inter alia*, the conjoining bond under discussion herein. The description is based upon analysis of the hyperfine structure of the electron density distribution[82].

An Account entitled 'Inverted geometries at carbon' discusses our theme including the small-ring [m.n.1]propellanes[83]. It is an excellent review of the subject, albeit misspelling my name. Any general references which I have not given are to be found therein.

Finally a paper on 'The C_1–C_3 bond in [1.1.1]propellane' has appeared[84]. The paper reviews the pertinent literature and describes *ab initio* methods applied by the authors to investigate the conjoining bond. They obtained 'a novel, non-axial orbital arrangement' which they term 'σ-bridged π', a pattern which appears to be characteristic of inverted configurations held together by short bridges. They show that 1,3-diborabicyclo[1.1.1]pentane (**101**) contains a BB bond almost identical with that in

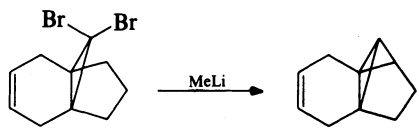
(101)

[1.1.1]propellane. The BB separation is predicted to be 1.61 Å. These molecules are compared in their 1,3-separations to bicyclo[1.1.1]pentane and 1,3-diazabicyclo[1.1.1]pentane.

Thus, we have the calculations and the theoretical discussions, and experimental results. After giving all of these the consideration which is their due, I hope that we shall merely need to wait for the conclusion of Wiberg's investigations[81b] (see above), rather than wait for Tishbi (the Prophet Elijah), to afford us a deeper understanding of the nature of bonding in the conjoining bond of small-ring propellanes.

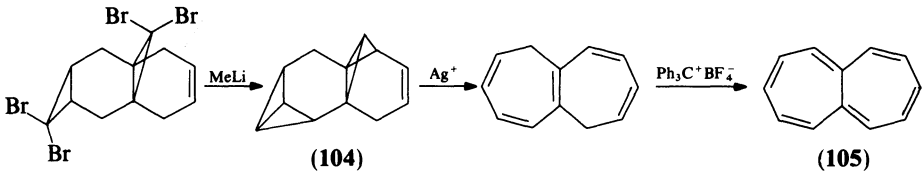
VII. MISCELLANEOUS STORIES

Regiospecificity has been studied in cyclopropylidene C–H insertion reactions within [m.n.l]propellanes, through carbenoid species when the dibromocyclopropane ring in such a propellane (e.g. **102**) was treated with methyl lithium. The formation of **103** involves a single insertion[85a].



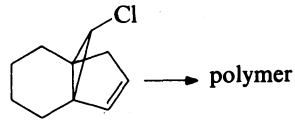
(102) **(103)**

Twofold insertion was also accomplished and just as **103** could be isomerized with Ag^+, heptalene (**105**) could eventually be obtained from **104**[85b].



(104) (105)

The different behavior of *syn*-(**106**) and *anti*-10-chloro[4.3.1]propell-7-enes (**107**) with *t*-BuOK in DMSO was interpreted in terms of disrotatory ring-opening in the former and a different mechanism in the latter[86].



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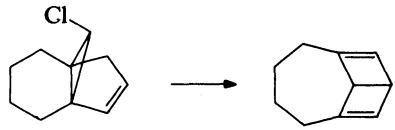
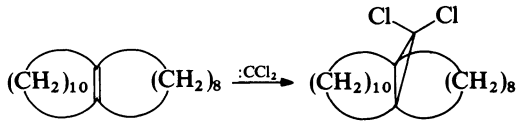


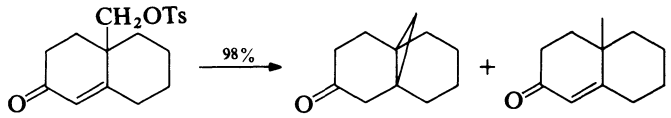
(107)

The *cis*-olefin but not the *trans*-betweenanene adds dichlorocarbene to afford the [10.8.1]propellane derivative **109**[87].



(108) (109)

An electrochemical reductive cyclization (see Section II) affords [4.4.1]propellan-3-one (**110**) in unusually high yield[88].

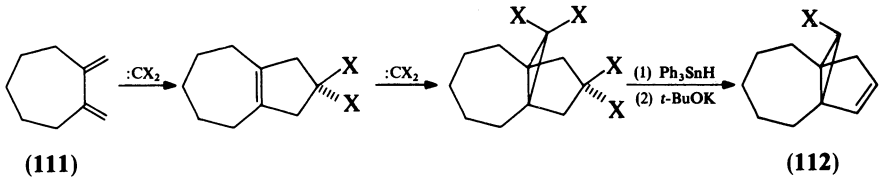


(110)

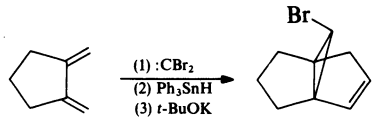
99 parts 1 part

An unusual 1,4-addition of a dihalocarbene to 1,2-bis-methylenocycloalkanes (e.g. **111** and **113**) gave bicyclic olefins which could then be converted into [5.3.1] (**112**) and [3.3.1]propellenes (e.g. **114**)[89].

The tosylhydrazone of [4.2.1]propellane-9-carboxaldehyde was converted into [4.2.2]propell-7-ene as a substrate for thermolysis[90].

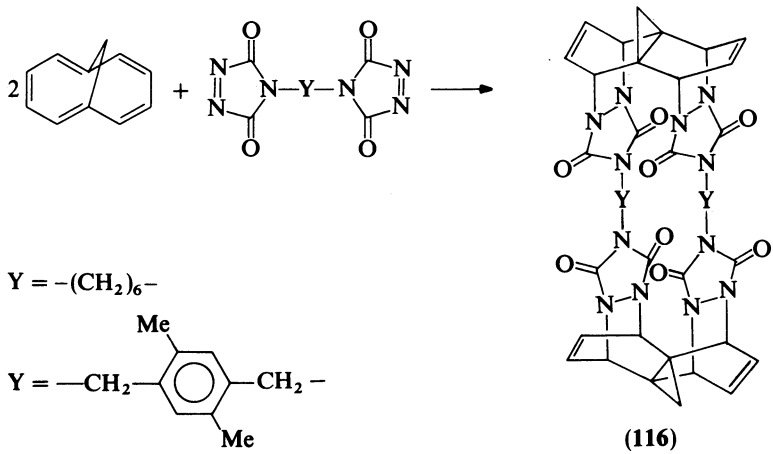


(111) (112)



(113) (114)

In the reaction of 1,6-methano[10]annulene with bis-triazolinediones the 2:1 adduct (**116**) has the following structure[91].



(116)

I have recorded[1-3] some 1500 references on propellanes. This chapter includes more than 100 references (including same 1984 references) on [m.n.l]propellanes without attempting exhaustive coverage. These numbers indicate that there is relatively much interest in those propellanes which form the title of this chapter.

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CHAPTER **21**

Cyclopropenes

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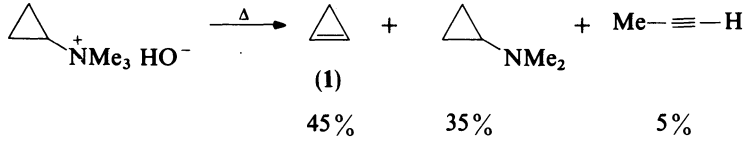
I. INTRODUCTION

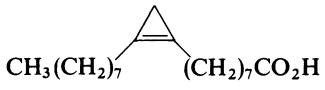
Although the first cyclopropane derivative was obtained[1] as early as 1881, and the parent hydrocarbon just one year later[2], it was not until 1922 that cyclopropene (**1**) became available. However, Freundler[3] (1897) claimed that the dry distillation of barium furoate led to cyclopropene in addition to furan, but the reaction proved difficult to repeat and the report remains unsubstantiated[4]. Work published by Dem'yanov and Doyarenko[5] in 1922 provided the first authenticated[6] synthesis of cyclopropene. These authors found that trimethylcyclopropylammonium hydroxide undergoes Hoffmann elimination by heating to approximately 300°C on platinized clay. This reaction, which parallels the original[7] synthesis of cyclobutene, was subjected to detailed scrutiny[6] in 1941 and under optimum conditions **1** was obtained in a yield of 45% (equation 1). Despite these early beginnings,



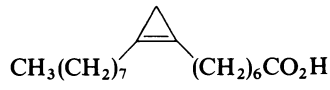
(1)

the chemistry of cyclopropene and its derivatives received little attention until the mid-1950s when the occurrence of cyclopropenes in nature was recognized and plausible routes to cyclopropenes became a reality with the advent of carbene chemistry[8,9]. Coverage for this contribution covers *Chemical Abstracts* up to the end of 1984.

Whilst the potential for synthesis of cyclopropene under volcanic conditions on primeval earth is recognized[10], the extent to which the ring system occurs in nature is known for only four classes of compounds, one of which involves cyclopropenone derivatives. Plants of the order Malvales contain varying amounts of the biologically active and homologous cyclopropene fatty acids sterculic acid (**2**)[11] and malvalic acid (**3**)[12]. The



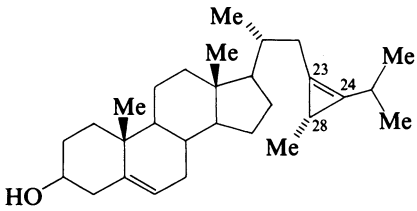
(**2**)



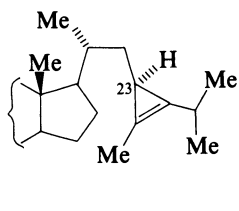
(**3**)

occurrence of these acids in the leaf and seed oils from the Malvaceae, Sterculiaceae, Bombacaceae and Tiliaceae (which include among others cottonseed and kapok seed oils, china chestnuts and some Malaysian edible seeds and nuts) families continues to attract attention[13]. The level of malvalic and sterculic acid in the oils varies[14] up to about 30% and does not necessarily decrease with cooking[15]. The biological effects of these naturally occurring materials on the growth of, e.g. trout[16] and the tobacco budworm[17], have been examined and improved methods for the assay of the acids continue to be sought[18].

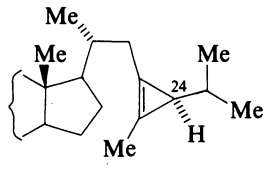
An extract of *Calyx nicaensis* has provided the three biologically active cyclopropene-containing marine sterols (28*R*)-calysterol (**4**), (23*R*)-23*H*-isocalysterol (**5**) and (24*S*)-24*H*-isocalysterol (**6**)[19–22]. Whilst calysterol (**4**) is the major isomer and the first of the series to



(**4**)

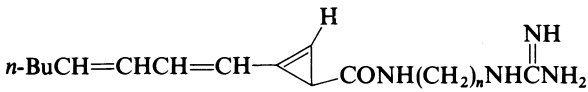


(**5**)



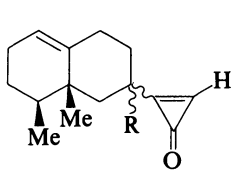
(**6**)

be isolated[19] it has yet[20] to be independently synthesized. A more unusual structural type is found in the marine species *Polyandrocarpa* sp.[23] and provides the third class of naturally occurring cyclopropenes. The polyandrocarpidines I (**7**) and II (**8**) are the major and minor components respectively and have antibacterial activity.

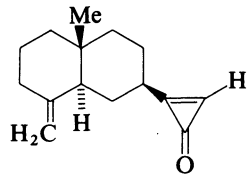


(**7**) $n=5$; (**8**) $n=4$

More recently[24] the naturally occurring cyclopropenones **9** and **11** have been isolated from *Telekia speciosa*. The terpene derivative with the 7α-H, compound **9**, is also found in *Lychnophora passerina* together with an isomer tentatively assigned as the 7β-H epimer **10** and not the eudesmane derivative **11** as initially thought.



(9) R = α-H
(10) R = β-H

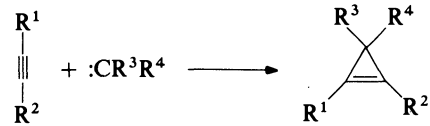


(11)

The uses to which synthetic cyclopropenes are being put augurs well for the future. Cyclopropene itself acts as an important chemical probe for *Azotobacter vinelandii nitrogenase*. The living cells reduce the hydrocarbon to a mixture of propene and cyclopropane in a ratio of about 2:1. The cyclopropene product ratio is important as a chemical probe for the nitrogenase and as an important new criterion for its biomimetic chemistry[25]. A copolymer of 1-methylcyclopropene and sulphur dioxide has found use[26] in audiovisual recording and in the preparation of integrated circuits whilst the employment of cyclopropenones as components of light-sensitive polymers for photographic and photothermographic processes has received attention[27]. As a vesicular photocopying material cyclopropenone derivatives are capable of forming a latent image by the liberation of carbon monoxide[28].

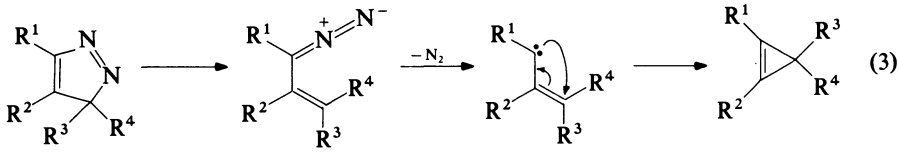
II. SYNTHESIS OF CYCLOPROPENES

The most commonly used methods for the synthesis of cyclopropenes fall into three categories. The addition of a carbene (or carbenoid) to an alkyne constructs the ring in a single step by the formation of two σ bonds (equation 2), but the concertedness or

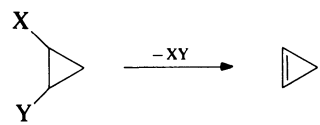


(2)

otherwise of the reaction is dependent upon the multiplicity of the carbene. The formation of an α, β-unsaturated carbene, a vinylcarbene, can be effected with comparative ease from either a 3*H*-pyrazole or an allylic diazo compound and, once formed, cyclization with concomitant π-bond migration ensues (equation 3). Probably the most used strategy employs 1,2-elimination from a (preformed) cyclopropane derivative (equation 4). These



(3)



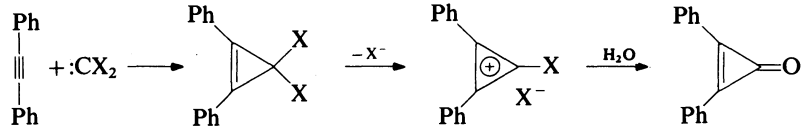
(4)

and other less common procedures are covered in the following pages. However, the methods employed for the synthesis of cyclopropenones and alkylidenecyclopropenes are grouped together in separate subsections for convenience and to provide a comprehensive section for each of these derivatives.

A. Addition of Carbenes and Carbenoids to Alkynes

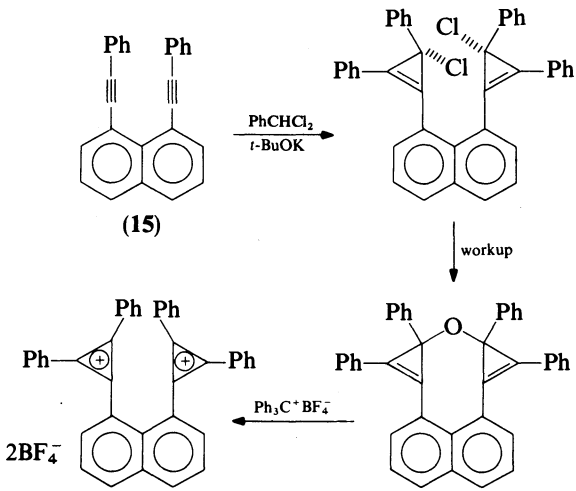
As already mentioned, the addition of a carbene to an alkyne provides a convenient and useful route to a good number of cyclopropenes (equation 2). The method is not restricted to free carbenes and syntheses with carbenoids and 'complexed' carbenes are well known. In general the method is limited by the stability of the divalent carbon species rather than the nature of the alkyne, although terminal alkynes and -ynols undergo insertion in competition with addition.

The ease and efficiency with which chloro- and bromocarbenes can be generated provides a ready route to 3- and 3,3-dihalocyclopropenes[29]. However, these compounds, e.g. **12**, easily lose halide ion to provide cyclopropenyl cations, e.g. **13**, which in turn lead to a variety of other derivatives notable amongst which are the products of hydrolysis, i.e. the



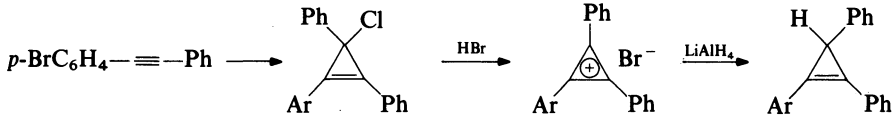
(12) (13) (14)

cyclopropenones, e.g. **14**. Thus phenylchlorocarbene adds[30] to the bis-alkyne (**15**) to give ether (**16**) which, with trityl tetrafluoroborate provides the bis-cation (**17**). The unsymmetrical diarylethyne (**18**) also adds phenylchlorocarbene[31]; treatment with HBr generates



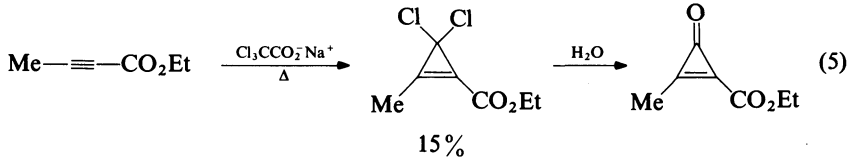
(15) (17) (16)

cation (**19**) which can be reduced to cyclopropene (**20**). Often the yields of these carbene addition reactions are not high but this disadvantage can be offset by the ready availability

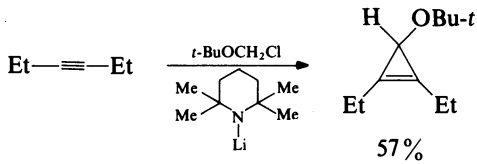


(18) **(19)** **(20)**

of the starting materials. The reactions depicted by equations 5[32] and 6[33] serve to illustrate this point.

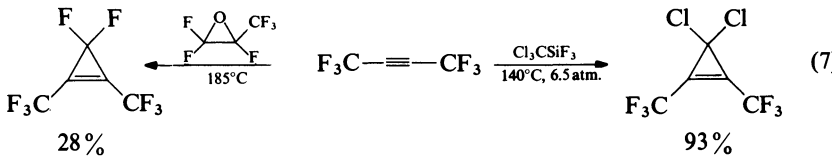


(5)



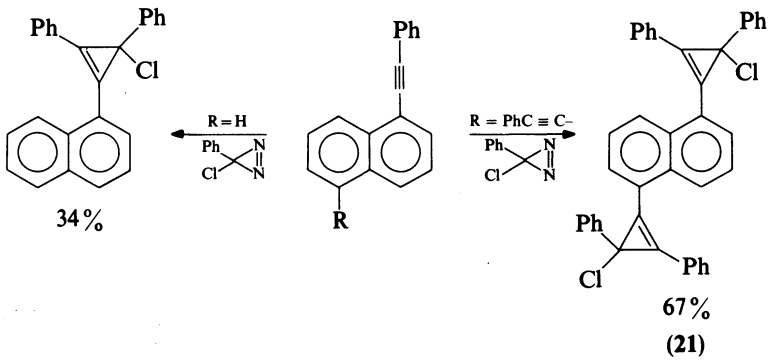
(6)

When the dihalocarbene is generated thermally or photochemically the product of cheletropic addition to the alkyne is usually isolable in adequate yield. For example, pyrolysis of (trichloromethyl)trifluorosilane at 140°C and 6.5 atm in the presence of perfluorobut-2-yne provides[34] 3,3-dichloro-1,2-bis(trifluoromethyl)cyclopropene in 93% yield. The corresponding perfluorocyclopropene is available from addition of difluorocarbene which can be generated by thermolysis of perfluoropropene oxide[35]



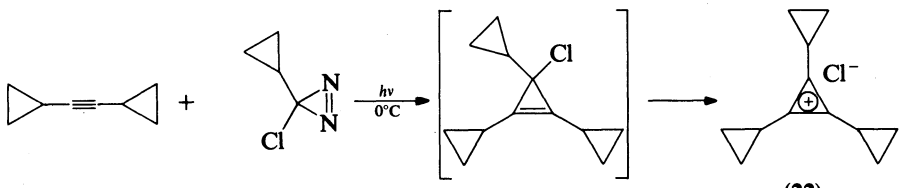
(7)

(equation 7). The thermal and photochemical decomposition of diazirines provides an alternative carbene source. Phenylchlorocarbene is available from this source and



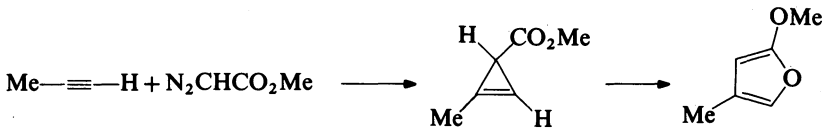
(21)

cyclopropenes such as **21** can be isolated in satisfactory yields. By comparison, the addition of photochemically generated cyclopropylchlorocarbene to dicyclopropylacetylene delivers product which undergoes facile chloride ion loss to yield the tricyclopropylcyclopropenyl cation (**22**) in 42% yield[36].

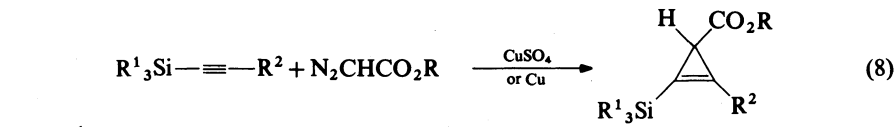


(**22**)

Carbalkoxycarbenes (or carbenoids) generated by the thermal, photochemical, or thermocatalytic decomposition of α-diazoesters provide a ready entry to 3-carbalkoxycyclopropenes upon addition to an alkyne[37]. With acetylene the carbenes derived from methyl or ethyl diazoacetate undergo insertion into the C–H bond as the principal reaction to give[38] propynoates in yields up to 50%; with propyne the same reagents give cyclopropenes in low yield. If copper oxide or copper sulphate are employed as catalysts the yields of the cyclopropene products generally increase but some cleavage of the three-membered ring is observed; with these simple alkynes copper oxide appears to be the better of the two



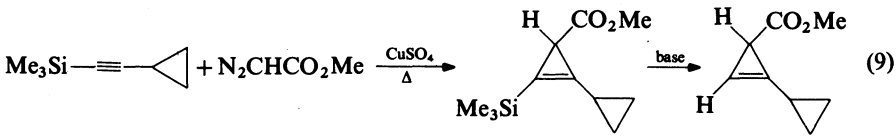
catalysts for cyclopropene synthesis. However, the most effective catalyst for a given substrate is not easy to predict and copper(II) oxide and sulphate, copper(I) chloride and bromide, and copper–bronze powder have often been employed (equations 8–11). The use



(8)

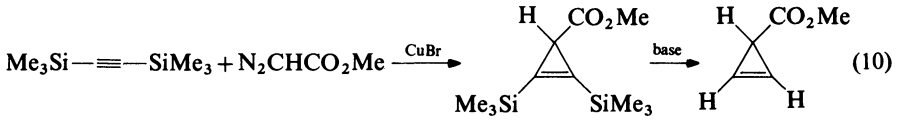
R^1 = Me or Bu-*n* R = Me or Et
R^2 = Me, Pr, or Bu-*t*

2–54% Ref. 39



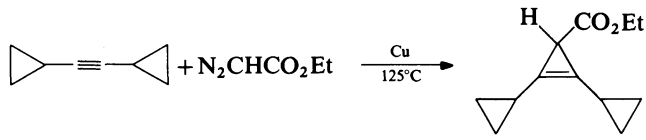
(9)

55% Ref. 40



(10)

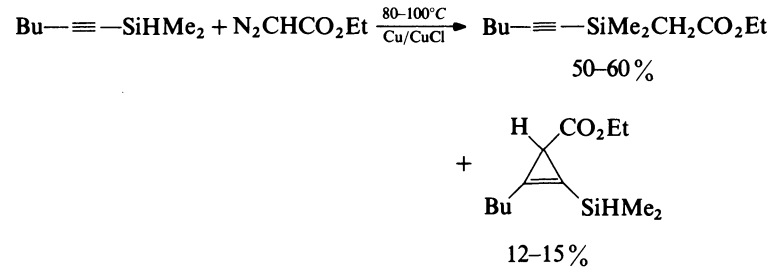
18% Ref. 41



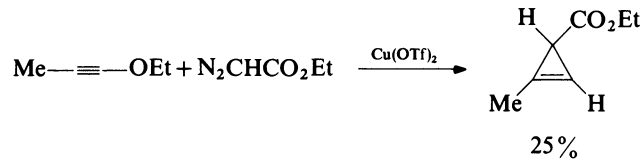
(11)

14% Ref. 42

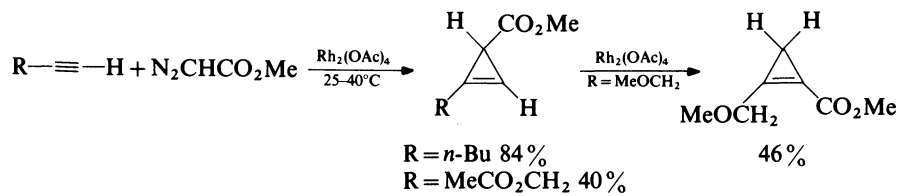
of labile silicon-based blocking groups to prevent C–H insertion have provided a viable route to terminal alkyne addition products from hydrolysis of the trialkylsilyl moiety after carbene addition (equations 9 and 10). The blocking group must be a trialkylsilyl derivative otherwise insertion of carbenoid into an Si–H bond occurs[43]. Copper(II) triflate has also



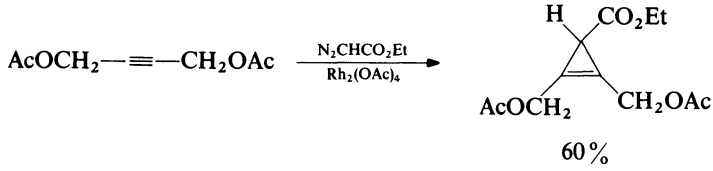
been employed[44] as a catalyst for diazoester decomposition but its effectiveness generally appears to be no better than the more commonly available reagents.



In the search for more efficient catalyst systems for diazoester additions several groups[45–47] have employed rhodium(II) acetate. Transition metal complexes have been widely used in cyclopropane synthesis but copper(I) triflate and palladium(II) acetate are ineffective for substituted ethenes. Rhodium(II) carboxylates have been shown[45a] to

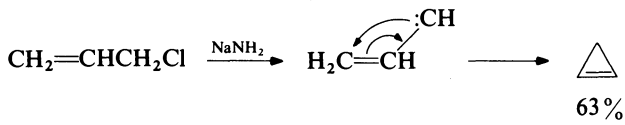


overcome these problems and their use has now been extended to cyclopropene synthesis. The reactions of methyl diazoacetate with terminal alkynes in the presence of rhodium(II) acetate provides synthetically useful yields of the appropriate cyclopropene. However, with rhodium(II) carboxylates carrying polar substituents a reduction in the efficiency of the reaction is observed. Sometimes the catalyst induces a rearrangement of the product cyclopropene as illustrated above. However, the use of a soluble rhodium(II) carboxylate (frequently the acetate) results in a 5–10 fold increase in the yield of the cyclopropene relative to those from copper(II) sulphate and copper–bronze powder and it is the catalyst of choice.



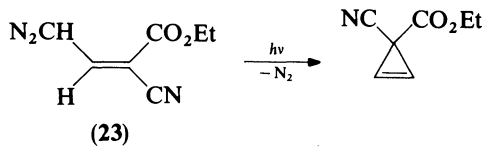
B. The Cyclization of α, β-Unsaturated (Vinyl) Carbenes

The rearrangement of a vinylcarbene to a cyclopropene is well known and provides a viable method for the synthesis of compounds whose substituents range from simple to complex. For example, base-induced α-elimination of HCl from allyl chloride provides a straightforward[48] synthesis of cyclopropene. Despite the availability of the parent



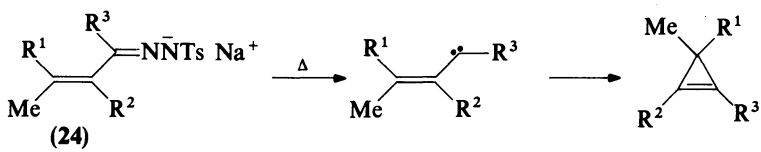
hydrocarbon by this method, the generation of substituted vinylcarbenes is better effected by other methods.

Because of the difficulty of their synthesis the deazetation of α-diazoalkenes has received little attention even though photolysis of **23** leads[49] to the corresponding cyclopropene



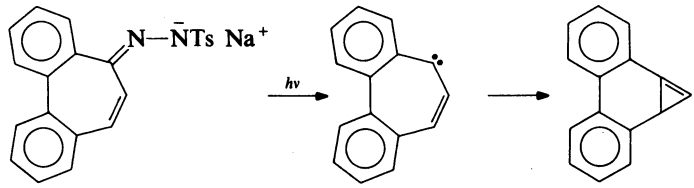
(23)

quantitatively. More commonly the thermal or photochemical decomposition of the sodium salt of the corresponding tosylhydrazone is used (equation 12) since these



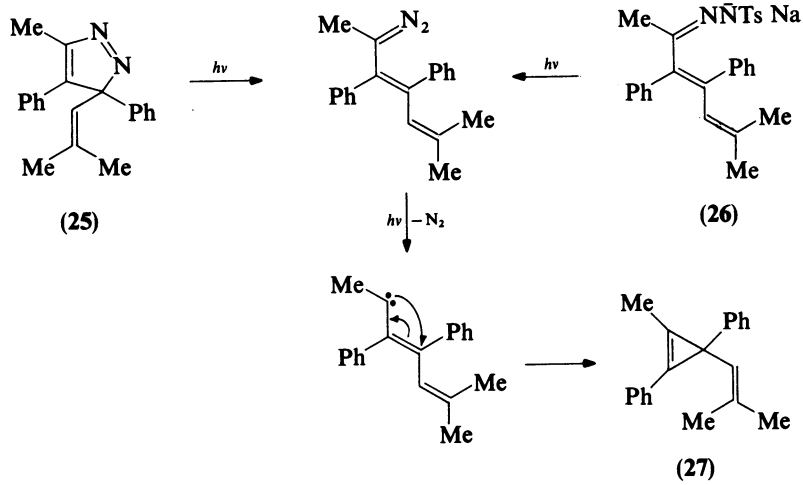
(24) (12)

compounds are readily available from the corresponding carbonyl compound. The reaction works well[50] for **24** when R^1 is other than hydrogen and the method is by no means restricted[51] to simple derivatives (equation 13).



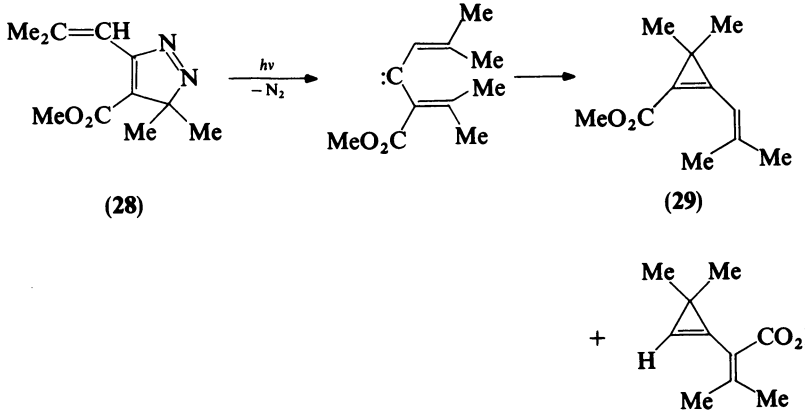
(13)

The most common source of α,β-unsaturated carbenes for cyclopropene synthesis is from the decomposition of 3*H*-pyrazoles which are, in turn, available from the addition of a diazo compound to an alkyne. On photolysis these compounds suffer ring cleavage to an α-diazoalkene prior to nitrogen loss and carbene formation. In this way cyclopropene **27** is available from either **25** or **26** by way of common diazo and carbene intermediates[52].



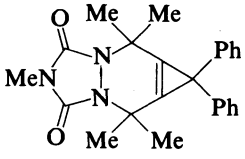
(25) (26) (27)

The mode of closure of the intermediate carbene is subject to steric constraints[53] as shown by **28** which delivers **29** highly regioselectively (> 90% yield); compound **29** is used



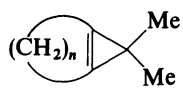
(28) (29)

as an intermediate for a stereospecific synthesis of chrysanthemic acid. The photodeazetation of 3*H*-pyrazoles has been used to provide a wide range of cyclopropene derivatives including compounds **30–34** illustrated below. The reaction is restricted to 3,3-di-



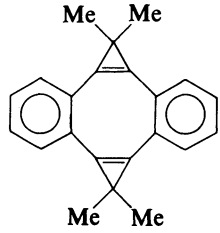
(**30**) 63%

Ref. 54



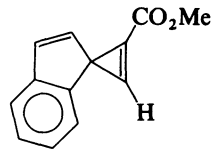
(**31**) $n=4$ 70%
(**32**) $n=5$ 84%

Ref. 55



(**33**) 1.8%

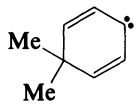
Ref. 56



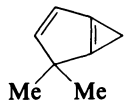
(**34**) 100%

Ref. 57

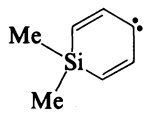
substituted pyrazoles because of tautomerism of the 3-monosubstituted compounds to the 1*H*-isomer. The unusual diazo compound **30** represents the smallest stable ring-fused cyclopropene known[54] and differs from hydrocarbon **31** which decomposes[55] at temperatures in excess of $-30°C$; homologue **32** is stable at room temperature. In this context it is interesting to note[58] that carbene **35** does *not* afford products by way of **36** whereas the silicon analogue **38** is an intermediate in the decomposition of **37**. Moreover,



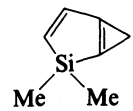
(**35**)



(**36**)



(**37**)

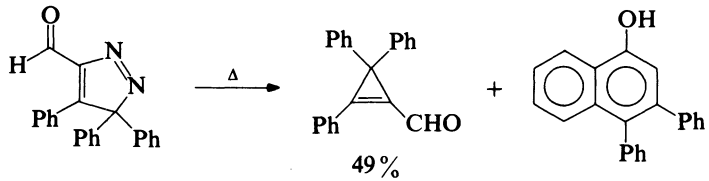


(**38**)

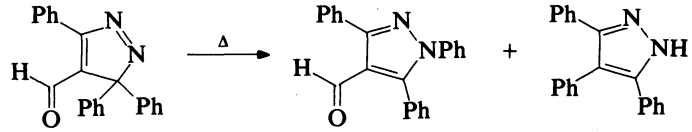
labelling studies have established[59] that bicycloheptene **40** is an intermediate in the dehydrohalogenation of **39**.

(**39**) (**40**) R = Ph 90%
R = Me 47%

Subjection of 3*H*-pyrazoles to thermolysis[60] often results in cyclopropene formation but competing reactions, the subtleties of which are not yet understood, interfere (equations 14 and 15). It is therefore the photochemical reaction which has received most

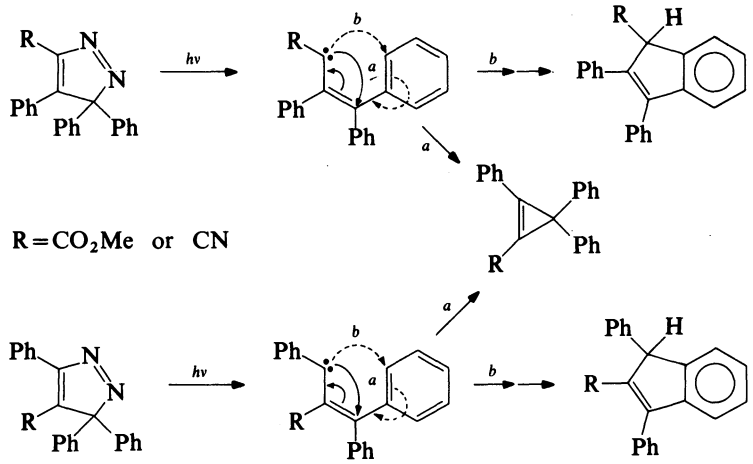


49% (14)



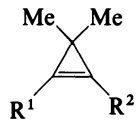
(15)

attention. When 3-phenyl-substituted 3*H*-pyrazoles (or the corresponding tosylhydrazones) are subjected to photolysis, competing reactions of the intermediate carbene (paths *a* and *b*, equation 16) ensue and indenes (path *b*) are also obtained[61-63]. Nonetheless, the



R = CO_2Me or CN (16)

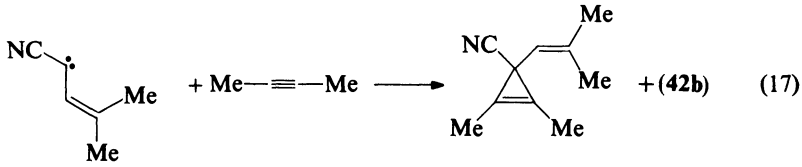
photodeazetation route, studied extensively by Franck-Neumann and his group[64-68], provides an excellent method for the synthesis of cyclopropene esters, e.g. **41**, and other



		Yield %	Ref.
(41)	**a**: $R^1 = R^2 = CO_2Me$	90	64
	b: R^1 = H; $R^2 = CO_2Me$	75	64
	c: R^1 = Ph; $R^2 = CO_2Me$	87	64
	d: R^1 = Ph; R^2 = CN	75	64
	e: $R^1 = n\text{-}C_5H_{11}$; $R^2 = CO_2Me$	91	64
	f: $R^1 = Me_2C(OH)CH_2$; $R^2 = CO_2Me$	100	65
			Ref.
(42)	**a**: R^1 = Ph; $R^2 = NO_2$		66
	b: R^1 = H; R^2 = CN		67
	c: R^1 = Me; R^2 = CN		67
	d: R^1 = H; $R^2 = p\text{-}MeC_6H_4S(O)$		68
	e: R^1 = H; R^2 = EtS(O)		68

derivatives of limited stability, e.g. **42**, the existence of which have been established by trapping reactions with dienes or 1,3-dipoles and/or by spectroscopic methods.

Interestingly, the carbene precursors to **42a–c** undergo competitive[66,67] intermolecular addition to alkynes to provide vinylcyclopropenes (e.g. equation 17). The sulphur-

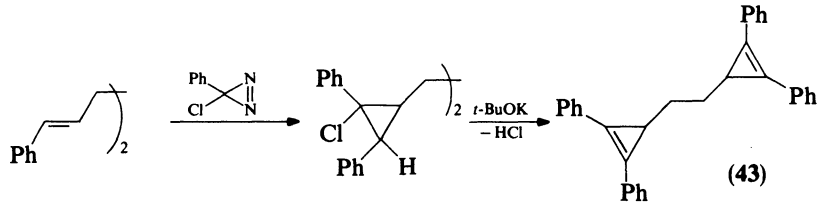


(17)

substituted derivatives **42d,e** are in equilibrium[68] with their carbene precursors in solution as evidenced by intermolecular addition to added alkenes; reactions with added alkynes have yet to be studied.

C. 1,2-Elimination Reactions

The introduction of unsaturation into a preformed, functionalized cyclopropane provided the first[5] authenticated synthesis of cyclopropene and the method continues[8,9] to find application in the synthesis of a wide range of derivatives. Nowadays the most commonly employed procedures involve dehydrohalogenation (but see below) with potassium *t*-butoxide as base as illustrated[69] for the 1,2-dicyclopropenylethane **43**. In

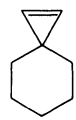


(43)

general the elimination is best performed in aprotic solvents such as tetrahydrofuran or dimethyl sulphoxide. The method provides for routine syntheses of tetrahalocyclopropenes[70] and 3,3-dimethylcyclopropene[71] amongst other derivatives[72–74] many more of which employ half-reduction of a dihalocarbene–olefin adduct prior to the elimination step[75–77]. The elimination reaction proceeds for both *cis* and *trans* disposed leaving groups but it is more efficient in the latter cases[78] as expected.

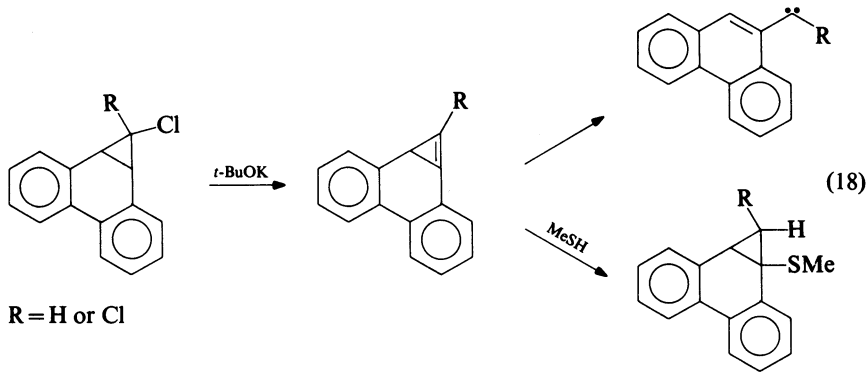
Many cyclopropenes unsubstituted at C(3) are unstable and nucleophilic addition to the π bond often occurs. Cyclopropene esters **44** are not capable of isolation[78] even when lithium dialkylamides are employed to effect the dehydrohalogenation reaction. Recent

(44)


(45)

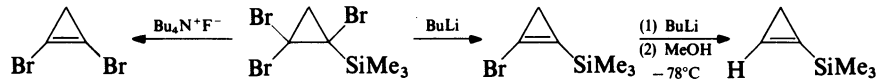
studies[79] have demonstrated that potassium *t*-butoxide supported on silica is effective for dehydrohalogenation and strained spiro-cyclopropenes, e.g. **45**, are available in good yield from passage of the halocyclopropane over the base-impregnated support at temperatures in the range 90–160°C. The potential of this process has yet to be fully explored.

The generation of strained bicyclo[4.1.0]hepta-1(7),2,4-trienes by the dehydrohalogenation route is now well established[80,81]. Although these molecules are highly reactive their presence has been established from nucleophilic addition reactions and by ring-opening to the corresponding aryl carbene (equation 18). The preparation of a number of



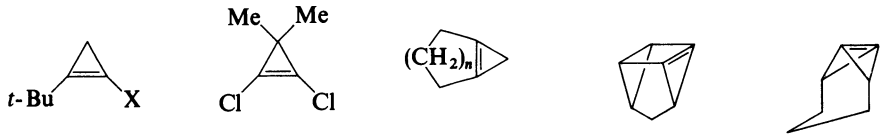
(18)

reactive but simple 1-halo and 1,2-dihalocyclopropenes has been described[82–84]. These generally unstable molecules can be used *in situ* in cycloaddition reactions and result from fluoride ion-induced removal of the elements of trimethylsilyl halide from the corresponding cyclopropane. Thus 1-bromo-[82], 1-chloro-[82], 1,2-dibromo-[84] and 1-bromo-2-chlorocyclopropene[83] are available. Moreover, with 1,1,2-tribromo-2-trimethylsilylcyclopropane halogen–lithium exchange can be effected[84] and the product 1-bromo-2-trimethylsilylcyclopropene is dehalogenated *in situ* (equation 19); each of the



(19)

cyclopropenes depicted in equation 19 is capable of undergoing $[_{\pi}4_s + {}_{\pi}2_s]$ cycloaddition with an appropriate diene. The 1,2-dehalogenation of a cyclopropane by an alkyl lithium[85–87] has had remarkable success in providing many reactive, highly strained, and



(46) X = Cl or Br — Ref. 85

(47) — Ref. 86

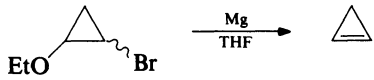
(40) $n=2$ **(48)** $n=1$ — Ref. 87

(49) — Ref. 88

(50) — Ref. 89

ring-fused cyclopropenes as illustrated by structures **46–48**, and the removal of HCl by butyllithium has provided compounds **49**[88] and **50**[89].

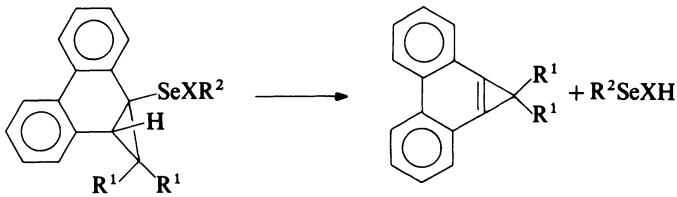
Other methods of forming the olefinic bond of a cyclopropene include the use of a Grignard reagent (equation 20)[90] and selenoxide elimination (equation 21)[91]. This



(20)

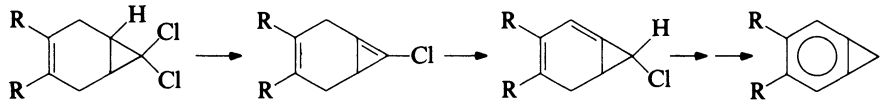
(21)

latter method[92] and variations upon it[84] have provided the elusive[80,93] cyclopropa[l]phenanthrene ring system from the dihydro derivatives **51**; the parent hydrocarbon[94] is stable only to −70 °C. In general the cycloproparenes[93] are available by



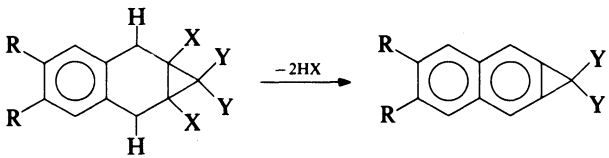
(**51**) **a**: $R^1 = Cl$; $R^2 = Ph$; X = O
b: $R^1 = H$; $R^2 = Me$; $X = CH_2^-$

two routes both of which involve dehydrohalogenation. The stable cyclopropabenzene[95] and cyclopropa[*b*]naphthalene[96] molecules are conveniently prepared by the bis-dehydrochlorination route depicted in equation 22. This so-called Billups sequence has



R = H or RR = benzo fusion (22)

been used extensively for the synthesis of various derivatives[93] but it is limited[83] to ring systems no larger than cyclopropanaphthalene. The second dehydrohalogenation method requires that the bis-elimination occurs outside of the three-membered ring (equation 23).

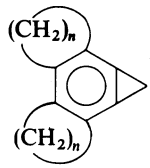


(23)

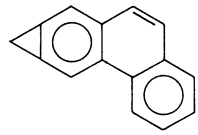
(**52**) R = H or RR = benzo fusion

In this way cyclopropa[*b*]naphthalene[97] and -anthracene[98,99] and their derivatives are available. The substrates **52** required for these latter cycloproparene syntheses are obtained

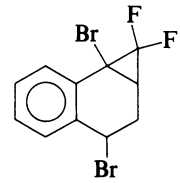
from the cycloaddition of an appropriate di- or tetrahalocyclopropene to a diene, often a quinodimethane; dehydrohalogenation with potassium *t*-butoxide then provides the cycloproparene in good yield. The tris-anelated benzenes[100,101] **53** and



(53) $n = 2$, 3, or 4



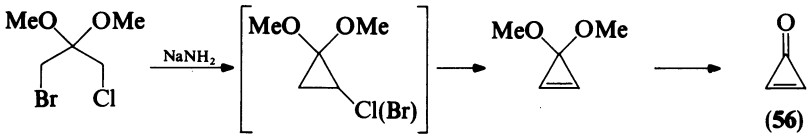
(54)



(55)

cyclopropa[*b*]phenanthrene[83] (**54**) have been prepared by this method. 1,1-Difluorocyclopropa[*a*]naphthalene[101], a molecule stable only below −30°C and unavailable by the routes outlined above, has been obtained by dehydrobromination of **55**.

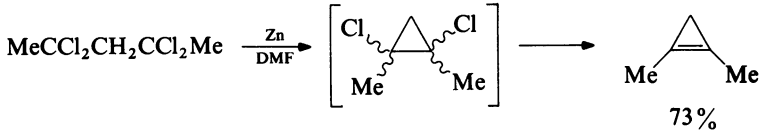
A number of cyclopropenes are available by routes which involve cyclopropanes as transient intermediates. For example, cyclopropenone dimethyl acetal[102] is obtained in yields up to 65% by sequential 1,3- and 1,2-elimination reactions (equation 24); the acetal



(24)

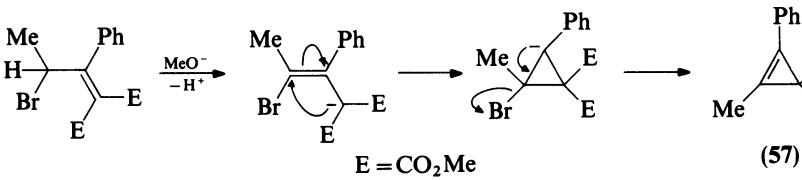
(56)

provides the parent enone (**56**) upon acid-catalysed hydrolysis. The very reactive dimethyl cyclopropene-1,2-dicarboxylate is available[103] by a strictly analogous sequence. The bis-dehalogenation of α,α,γ,γ-tetrahaloalkanes by zinc in dimethylformamide (DMF) pro-



73%

vides[104] various cyclopropenes in fair to good yields as illustrated for the 1,2-dimethyl derivative. Finally, the cyclopropene **57** has been obtained[105] in low (19%) yield by the pathway depicted in equation 25.



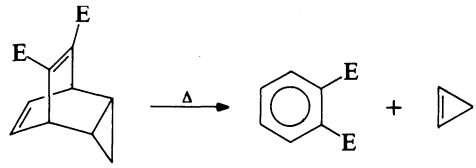
(25)

E = CO_2Me

(57)

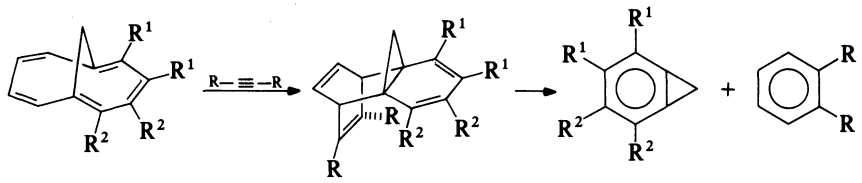
D. Alder–Rickert (Retrodiene) Cleavage

Alder–Rickert (retro Diels–Alder) cleavage of the formal cyclopropene adduct **58** (prepared by cycloaddition between norcaradiene and dimethyl acetylenedicarboxylate)



(58) $E = CO_2Me$

proceeds in a quantitative fashion as evidenced[106] by the yield of phthalic ester formed. However, cyclopropene is isolated in only 1% yield due to its ready polymerization under the reaction conditions. Although the strategy depicted by this synthesis has not found application in the generation of other simple cyclopropenes, Vogel and his group have developed[94, 107, 108] the procedure to provide viable pathways to the cyclopropparenes.



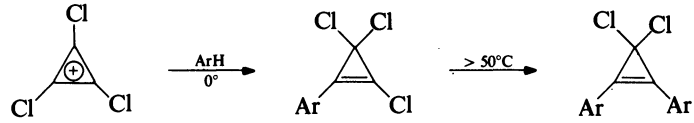
(59) (60) (61)

a: $R^1 = R^2 = H$;
b: $R^1 = H$, R^2R^2 = benzo fusion;
c: $R^1R^1 = R^2R^2$ = benzo fusion

Thus cyclopropabenzene (**61a**) can be obtained[107] in 45% yield from flash-vacuum pyrolysis of the Diels–Alder adduct **60a** formed from 1,6-methano[10]annulene (**59a**) and dimethyl acetylenedicarboxylate. In like manner the benzo analogue **59b** provides cyclopropa[*a*]naphthalene (83%)[108] and the dibenzo derivative **59c** gives cyclopropa[*l*]phenanthrene[94]. Whereas **61a** and its 'linear' naphtho[*b*] analogue are stable entities, **61b** suffers explosive decomposition on melting and **61c** decomposes at temperatures in excess of −70°C.

E. Miscellaneous Cyclopropene Syntheses

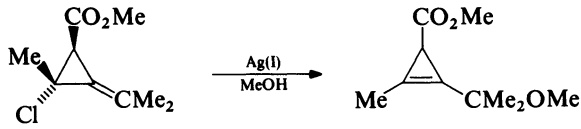
Cyclopropene and its deuterium-labelled derivatives can be obtained by the photodecarbonylation of the corresponding furan[109] at 254 nm but the method is of strictly limited value because of the photolability of many cyclopropenes (Section IV.B.2). West and his coworkers[110] have shown that aryltrihalo- and diaryldihalocyclopropenes are available from classical Friedel–Crafts aromatic substitution reactions employing the cyclopropenyl cation as electrophile. Thus tetrachlorocyclopropene is converted to its derived cation which is then allowed to react with an aromatic compound. The exothermic reaction provides monoarylcyclopropene at low (~ 0°C) temperature and the diaryl derivative at higher (> 50°C) temperature (equation 26). In this way 2-phenyl-1,3,3-trichlorocyclopropene can be obtained in 58% yield and the *p*-fluorophenyl analogue in



(26)

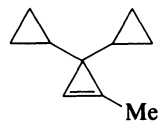
54% yield. These compounds can be treated separately to provide the diaryl derivatives. However, strongly activated aromatics yield triarylcyclopropenium ions. The reaction has received considerable attention particularly because hydrolysis of the gem-dichloro derivatives provides an excellent route to the corresponding cyclopropenones (see Section II.F.). Moreover, the reaction is not limited to aromatic compounds as the nucleophilic component and preparation of nitrogen-, sulphur- and selenium-substituted compounds en route to cyclopropenylimines, -thiones and -selenones is well documented and discussed under cyclopropenone synthesis below.

A different synthesis of cyclopropenes employs methylenecyclopropanes carrying a good leaving group as a ring substituent. For example, the 2-chloro derivative **62** leads[37b] to **63** by silver(I) ion assisted ionization and nucleophilic capture of the resulting allylic



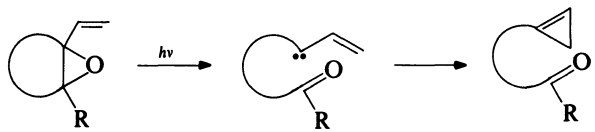
(62) **(63)**

cation at the exocyclic carbon atom. A similar reaction, but involving reductive dechlorination of the 1-methylene-2,2-dichloro precursor[111] leads to **64** in 14% yield.



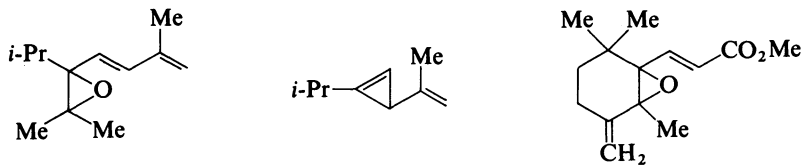
(64)

Long-chain cyclopropenes and cyclopropene esters are produced upon photolysis of α,β-unsaturated epoxides[112] as illustrated by equation 27. Whilst vinylcarbenes are the



(27)

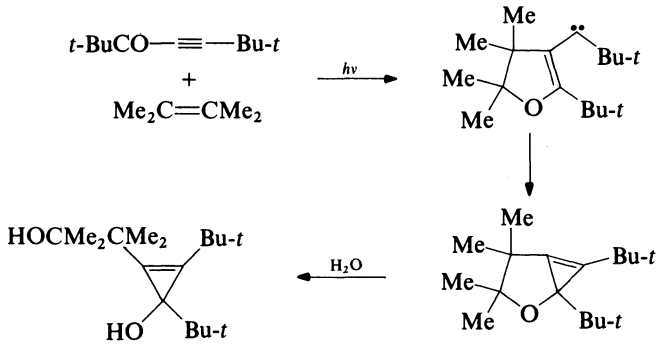
presumed intermediates the reaction is included here since it represents a more unusual approach to such carbene species. The method provides vinylcyclopropene **66** in 26% yield from **65**, but analogous photolysis of **67** provides a complex mixture of products



(65) **(66)** **(67)**

which include five cyclopropenes; the potential of the method has yet to be delineated. A vinylcarbene is also the presumed intermediate[113] in the high yield (91%) synthesis of

cyclopropenol **68** which results from [3+2] photocycloaddition and solvolysis (equation 28).

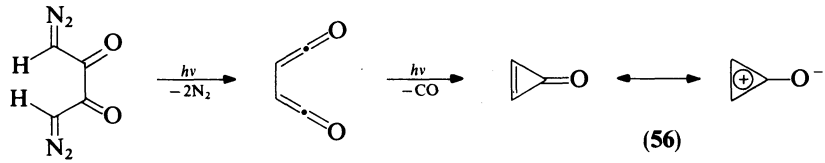


(28)

(68)

F. Synthesis of Cyclopropenones and Derivatives

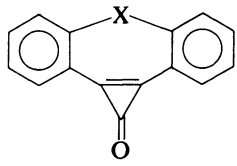
The chemistry of the resonance-stabilized cyclopropenone (**56**) and its derivatives has been the subject of three reviews[114] each of which has encompassed the synthetic procedures employed. The parent unsubstituted molecule (**56**) is readily available from 2,3-dichloropropene via 1,1-dimethoxycyclopropene (cf. equation 24)[102] and is stable for long periods when stored under inert gas at temperatures below its melting point of −29°C. Although the acid-catalysed hydrolysis of the acetal as the final step of the sequence proceeds in ~ 90% yield, the overall yield from the dichloropropene is about



(56)

25%. Compound **56** has also been generated photochemically[115] and isolated by matrix methods.

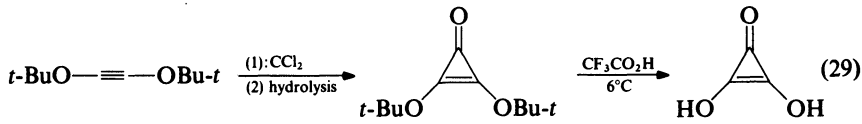
The 1,3-elimination route to cyclopropenone developed by Breslow[116], and the route by which **56** is normally obtained (equation 24), still finds application[114] and is an excellent preprative method. Thus diadamantyl derivatives[117] and the ring-fused cycloheptatrienes **69**[118] are available.



(69)

X=CO, CH_2, CHMe, CHEt

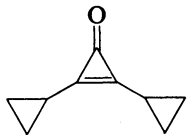
The method by which cyclopropenones were first prepared[119], namely the addition of dichloro (or dibromo) carbene to an alkyne and subsequent hydrolysis of the adduct continues[32] to be a good source of cyclopropenones despite the generally low yields involved. In particular, it has provided[120] a convenient synthesis of deltic acid (**70**) in 13–35% overall yield from di-*t*-butoxyacetylene (equation 29). The dicyclopropyl



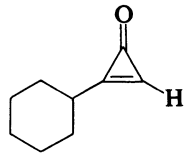
(29)

(70)

compound **71**[36,121] and the first fully characterized monosubstituted derivative **72**[24] have been obtained by this method. The latter compound has provided spectroscopic data for

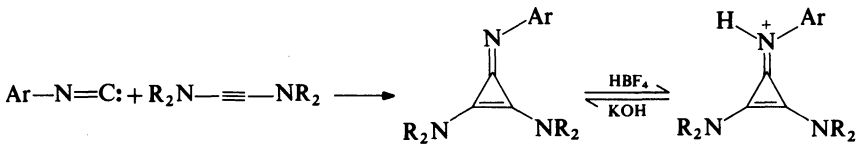


(71)



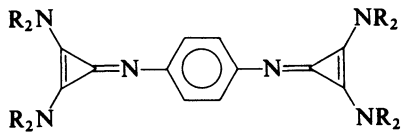
(72)

comparison with the naturally occurring cyclopropenones **9**–**11** (Section I). A variation upon the general method[122] outlined above involves the addition of isocyanides to ynediamines to yield the corresponding cyclopropenone imines **73** in yields of 20–74%. The reaction is accelerated by electron-withdrawing substituents in the *para* position of the



(73)

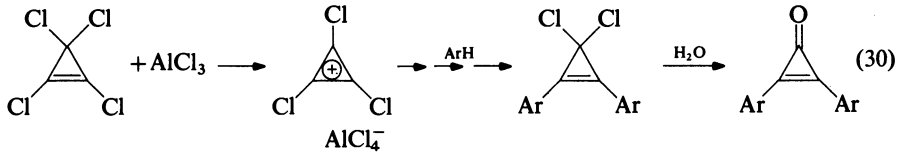
aromatic ring and the products are protonated at the imino nitrogen atom upon reaction with fluoroboric acid; aroylisocyanides also undergo the reaction. With an excess of alkyne, bis-isocyanides provide bisimines **74**.



(74)

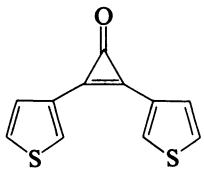
The use of perhalocyclopropenes, and particularly tetrachlorocyclopropene[70], in the preparation of cyclopropenones and their derivatives is important. Deem[123] has reported a convenient, high yielding (71%) synthesis of diphenylcyclopropenone and this, and the following reactions, proceed by way of an ionization–cation capture sequence which works

well for aromatic substrates (Friedel–Crafts reaction) that contain weakly activating groups (see Section II.E). Hydrolysis of the gem-dichloride completes the sequence (equation 30). When this procedure is applied to the synthesis of dichlorocyclopropenone a

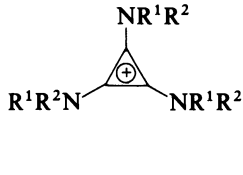


(30)

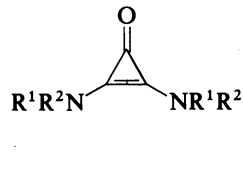
particularly careful hydrolysis is needed due to the highly unstable nature of the product[124]. Stable derivatives obtained by this method include bis-(9-anthryl)- and bis-(*p*-cyclopropylphenyl)cyclopropenones[125,126] and the more unusual bis-(2-thienyl) analogue **75**[127].



(**75**)

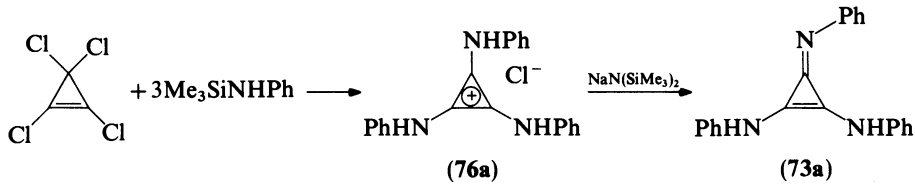


(**76**)



(**77**)

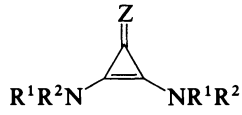
The nucleophilic capture of the trichlorocyclopropenium ion is not restricted to aromatics. In fact treatment of tetrachlorocyclopropene with secondary amines and thiols results in tris-amino-[128] and thio-[129] cyclopropenium ions, e.g. **76**. One advantage of such species is in their reaction with nucleophiles, e.g. HO^-, which deliver the corresponding sp^2-hybridized derivative, e.g. enone **77**, by an addition–elimination sequence[130]. The transammination reaction, initially[128] performed in good-to-excellent yields with secondary amines, often employs a trimethylsilylamine which has allowed[131] for the synthesis of the tris-(mono-organylamino)cyclopropenium salt (**76a**) in almost quantitative yield.



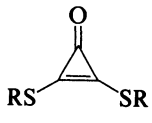
(**76a**) (**73a**)

Deprotonation of **76a** can be effected and imine **73a**, the first aza-analogue of deltic acid (**70**), is obtained in 72% yield. Compound **73a** is stable for long periods at −30°C but at ambient temperatures decomposition is complete in a period of days. In this way a range of resonance-stabilized cyclopropenones, cyclopropenethiones and cyclopropenimines can be conveniently prepared as illustrated by compounds **77**–**80** over page[130–133].

By employing a 1-aryl-2,3,3-trichlorocyclopropene (easily available from tetrachlorocyclopropene—see equation 26) an analogous sequence of reactions can be performed to give the corresponding aryl-substituted derivatives. In particular the aryldiaminocyclopropenium ions (**81**) have provided a wide range of derivatives[134–139] in yields ranging from 60 to 95% as illustrated by equation 31.

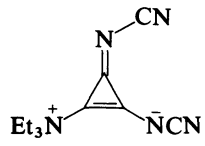


(77)	Z = O		(78)	Z = S	Ref.
	91%	$R^1 = R^2 = Me$		—	132
	81%	$R^1 = R^2 = Et$		—	132
	80%	$R^1 = R^2 = i\text{-}Pr$		80%	130
	22%	$R^1 = Me$; $R^2 = Ph$		96%	130



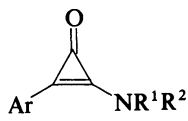
(79)

R = *t*-Bu Ref. 130

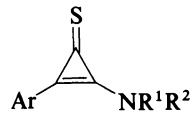


(80)

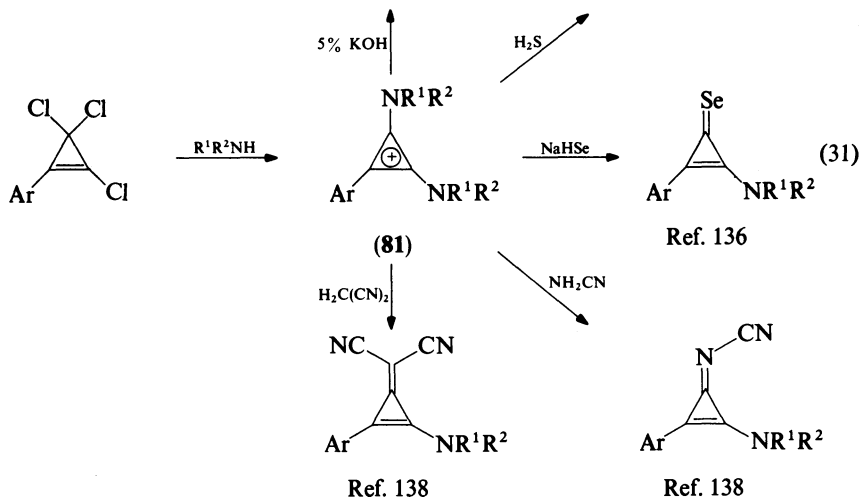
66% Ref. 133



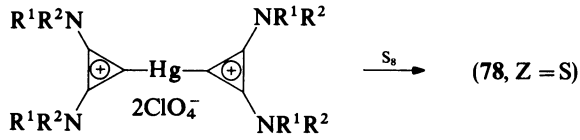
Refs 134, 135



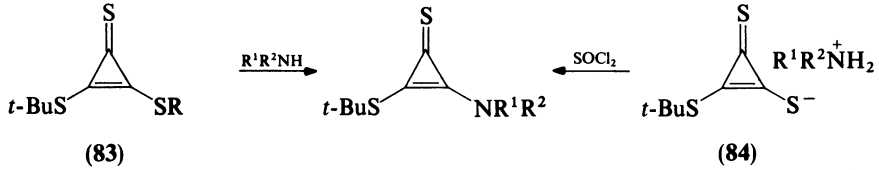
Refs 134–137



Analogous, but less common, syntheses have employed[139] the mercury(II) complexes **82** which provide cyclopropenethiones **78** (Z = S). The replacement of the thioalkyl substituent of compound **83** occurs upon treatment with a secondary amine[140] and a limited range of aminothiocyclopropenthiones are available in excellent yields. Moreover, these same compounds result from reaction of the corresponding thiolate (**84**) with, for example, benzoyl or thionyl chloride (equation 32). Such compounds have possible application in medicine, as dyes and as agrochemicals.



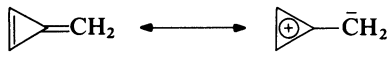
(82) $R^1 = R^2 = i$-Pr or R^1 = Me; $R^2 = t$-Bu



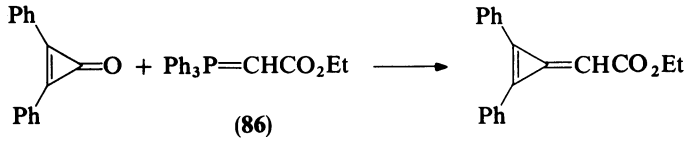
(32)

G. Synthesis of Methylenecyclopropenes (Triafulvenes)

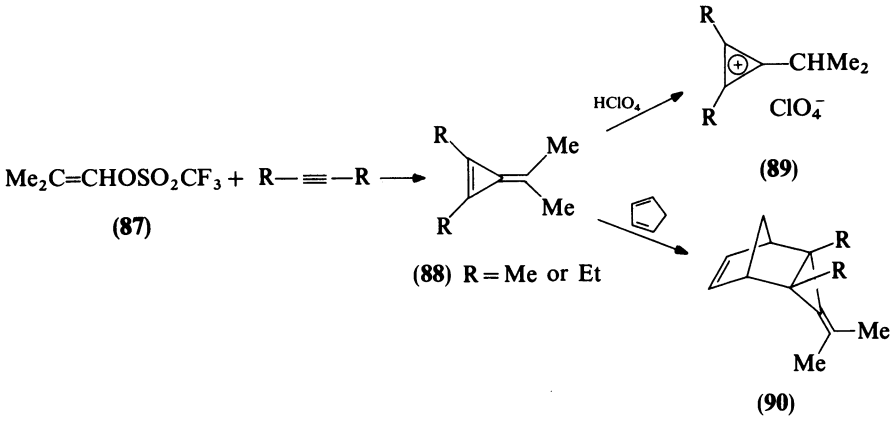
Because the stabilization energy of methylenecyclopropene (**85**) is considerably less than that of cyclopropenone (1 vs. 1.36 β) much of the early synthetic work[114, 141] on the former



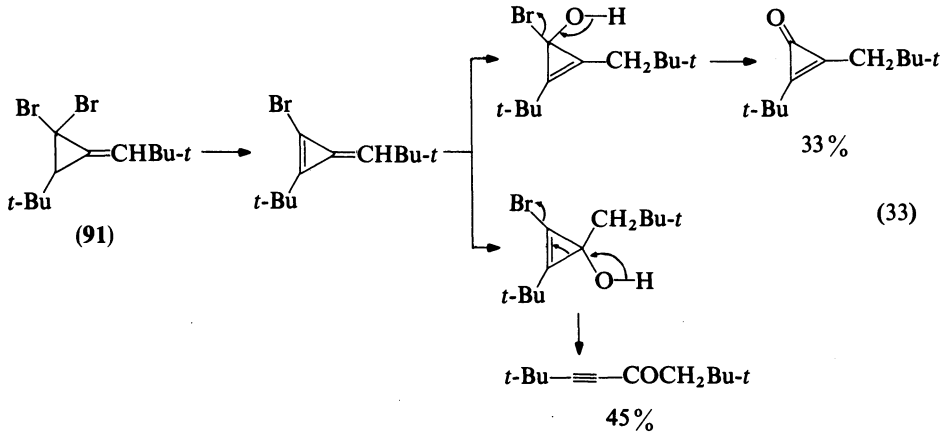
system concentrated upon the preparation of derivatives carrying stabilizing electron-withdrawing substituents at C(4). For example, one of the earliest[142] syntheses involved a



Wittig reaction between ylid **86** and diphenylcyclopropenone. More recently methylenecyclopropenes carrying alkyl substituents have been prepared and characterized in

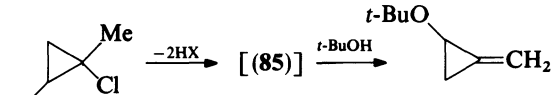


solution. Addition of the carbene[143] derived from vinyl triflate **87** to but-2-yne or hex-3-yne provides the simple alkylidene compounds **88** which were characterized as the corresponding cyclopropenium perchlorate **89** and Diels–Alder cycloadduct **90**. Dehydrobromination of the isomeric methylenecyclopropanes **91** can be effected[144] and the corresponding triafulvenes have been characterized in solution spectroscopically and by hydrolysis at $-10°C$ (equation 33).



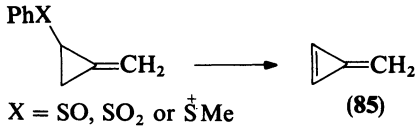
(33)

By commencing with a dihalocyclopropane Billups and his group[145] were able to provide support for the existence of parent compound **85** as evidenced by nucleophilic addition of *t*-butanol to give the methylenecyclopropane (equation 34) in 37% yield. A



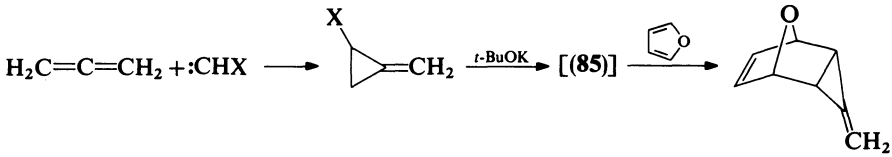
(34)

complex series of elimination–rearrangement sequences are likely to be involved in the conversion **92** → **85** because of the various 1,2-elimination pathways available. Compound **85** is also produced by base-catalysed elimination of phenylsulphinic or -sulphonic acid or phenyl methyl sulphide from the appropriate methylenecyclopropane (equation 35)[145, 146]. The addition of halocarbene to allene and subjection of the product

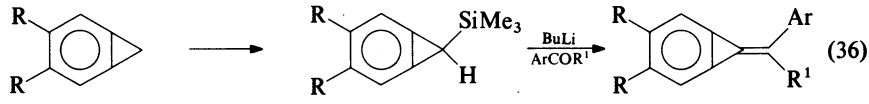


(35)

to dehydrohalogenation has provided unequivocal[147] evidence for the formation of **85** as determined from spectroscopic measurements and trapping experiments. The NMR data



reported[148] are remarkable for their thermal stability. The compounds are prepared by a modified Peterson olefination procedure (equation 36) which provides products in generally high yields.



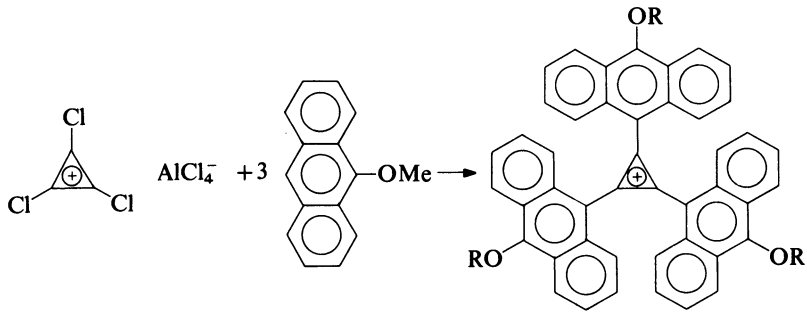
(36)

R = H or RR = benzo fusion

(93)

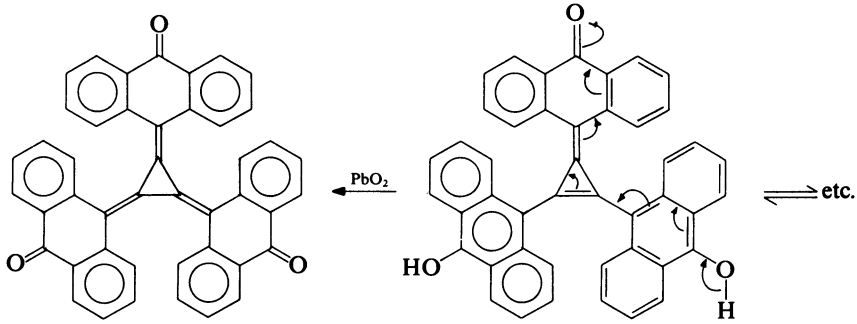
Ar = Ph, *p*-$MeOC_6H_4$–
R^1 = Ph, CF_3, Me, H

Of the possible methylenecyclopropene derivatives the 'quinocyclopropenes', e.g. **96**, represent an interesting class of the cross-conjugated system[114]. Moreover, these



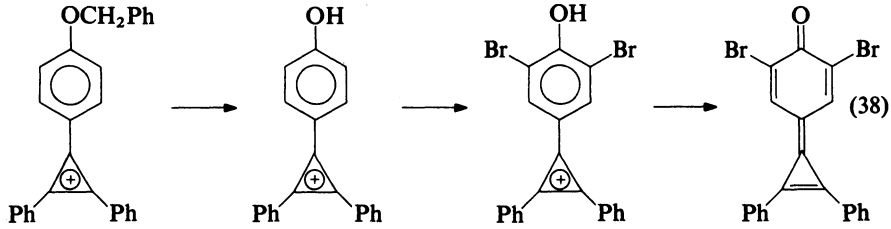
(94) R = Me
(95) R = H

(37)



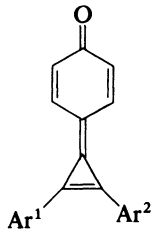
(97) (96)

molecules have attracted attention[149–152] since oxidation leads to the fully conjugated 'stretched-out' anthraquinone species[47] with potential as dyes, photoconductors and photographic materials. The usual route to these compounds employs the trichlorocyclopropenyl cation in Friedel–Crafts alkylation with an aromatic ether as illustrated for the formation of the tris-(9-anthryl) system **94** (equation 37)[149]. Demethylation with boron tribromide provides triphenol **95** which then loses a proton to give quinocyclopropene **96**, a molecule stabilized by tautomerism. Subsequent oxidation leads to the fully conjugated [3]radialene derivative **97**. The first methylenecyclopropene isolated[150] (equation 38) is an analogue of compound **96**. The reaction sequence is general but works

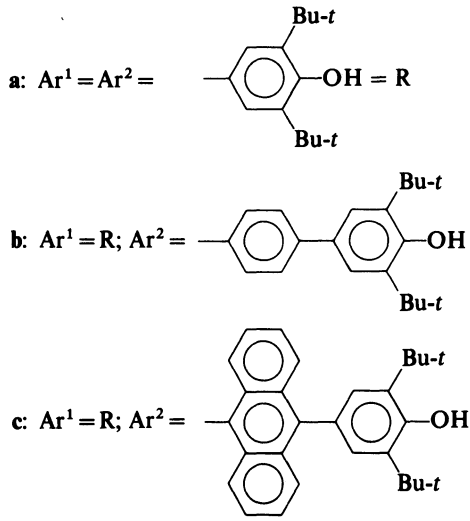


(38)

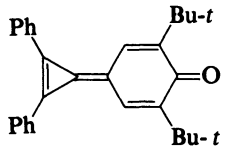
best when a 2,6-disubstituted aromatic ether is employed; a wide range of derivatives is available[114] as exemplified by **98**[151]. Simpler derivatives are easily obtained from the



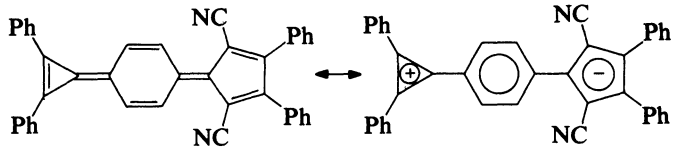
(98)



appropriate cyclopropenium ion as illustrated[114] by **99**[152] and **100**, the latter[153] system deriving considerable stabilization from the charge-separated form.

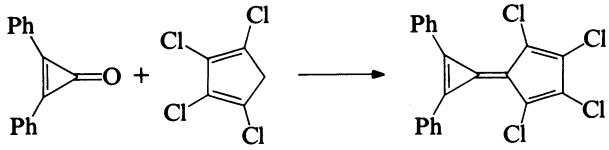


(99)



(100)

Simple calicenes[141] are available from the condensation of a cyclopropenone with a cyclopentadiene or an indene (equation 39) or by reaction of a cyclopropenyl cation with a



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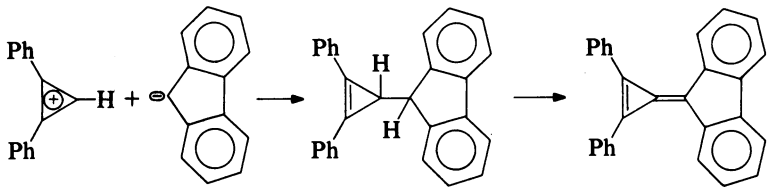
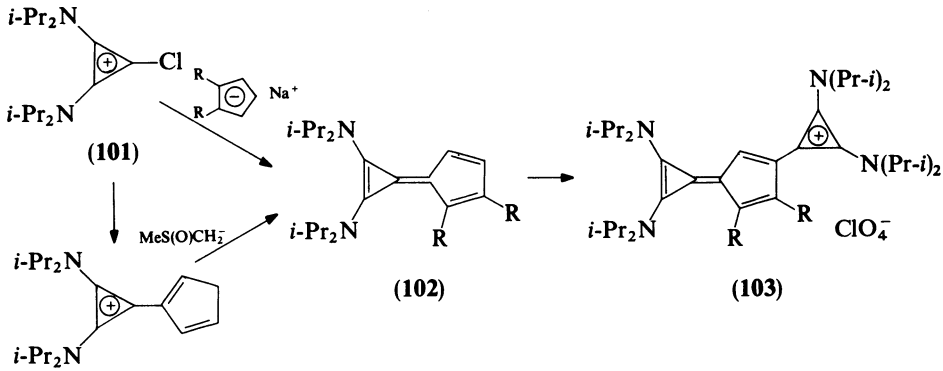


(40)

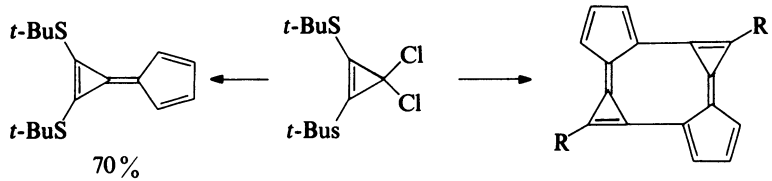
cyclopentadienyl anion (equation 40). Recent emphasis[154–161] has been directed towards the synthesis of novel derivatives of various types. For example, reaction of cation **101** with sodium cyclopentadienide provides[154] salt **103** (R = H) in 54% yield. The reaction



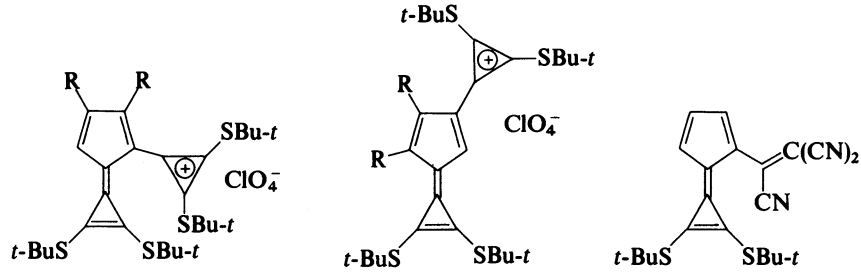
proceeds by way of the reactive calicene **102** (R = H) which has been isolated[155] from use of controlled quantities of cyclopentadiene followed by proton abstraction with the dimsyl anion. Yoshida[156] has produced the parent diamino-substituted triafulvene by hydride ion

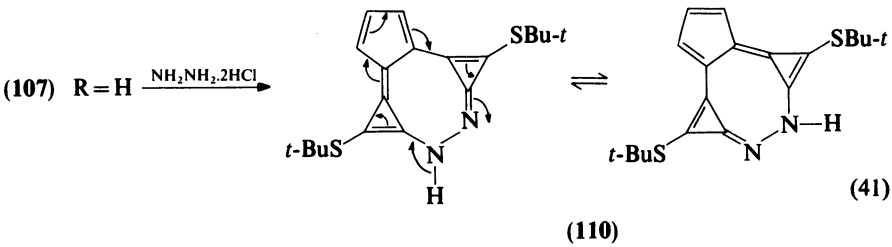
(104)

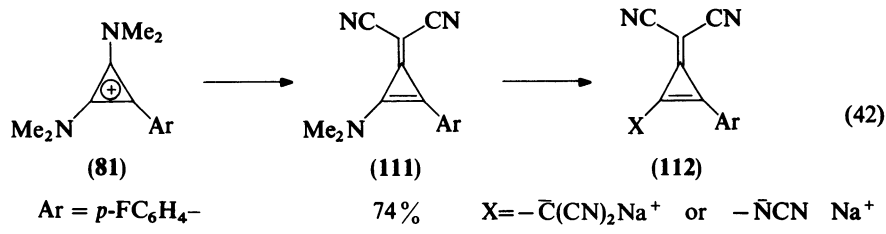
abstraction from **104** and he and his group have expended considerable effort in providing thio-substituted analogues. By employing[157] 1,2-bis-*t*-butylthio-3,3-dichlorocyclopropene (available from the thioketone and thionyl chloride) the thio-substituted calicene **105** can be obtained in high yield. With excess cyclopentadienide[158] the cyclic



bicalicene **106a** is produced albeit in low (5%) yield. The latter compound has been converted into the corresponding tin(IV) derivative **106b** and the parent hydrocarbon **106c**. This latter compound is stable for a period of weeks at room temperature, exhibits normal chemical shifts for its protons and carbon atoms in the NMR spectra, and shows no bond length alternation around the periphery. Consequently, there is no contribution from the 16π electron system and the molecule has been termed a 'peripheral 16π aromatic







system'. Similar studies have now[159] provided the biscyclopropenyl systems **107** and **108**, compound **109**[160] and the azathio species **110** (equation 41)[161].

Less complex triafulvenes with heteroatom substituents are also available. Thus cation **81** condenses[138] with dicyanomethane to give **111** which can be converted, in turn, to the fully conjugated anions **112** (equation 42).

III. PHYSICAL AND THEORETICAL ASPECTS OF CYCLOPROPENES

Cyclopropene has attracted the attention of both the theoretical and the experimental chemist because of its special place as the smallest unsaturated cyclic molecule. Whereas the ring strain[162] of cyclopropane is ca. 118 kJ mol^{-1} that of cyclopropene[163, 164] is ca. 228 kJ mol^{-1} and the molecule is a good dienophile in [4 + 2] cycloaddition reactions which reduce the strain energy by ca. 110 kJ mol^{-1} (Section IV.A.6.c). These observations suggest that the π bond is weak. However, the fact that the C=C length[165] is short (129.6 pm) and its infrared vibrational frequency high (1641 cm^{-1})[9] argues against this. It is generally held[162] that the additional strain energy of cyclopropene over its saturated analogue is localized in the σ framework with increased angular strain at all three carbon atoms contributing significantly; the C(1) C(2) C(3) angle is[9, 165] 51° and the C(1) C(3) C(2) angle 64.5°.

An analysis of the structural data of 34 cyclopropene derivatives[166] has led to the conclusion that the vinylic carbon atoms of cyclopropene use $sp^{1.19}$ hybrid orbitals in bonding to substituents and $sp^{2.68}$ hybrids to the ring σ framework. *Ab initio* calculations at the STO-3G level[167] show that σ-donating, π-withdrawing, and most π-donating substituents stabilize strained molecules including cyclopropene; σ-withdrawing substituents destabilize the unsaturated linkage. Such calculations performed for cyclopropene with the basis sets STO-3G, 4-31G, 6-31G* and 6-31G** provide [168] satisfactory values for the enthalpy of rearrangement to propyne and yield strain energies and geometries in accord with experiment. Indeed, because of the special place taken by cyclopropene as an unsaturated monocycle, many calculations have been performed in order to assess the limits of the theoretical model in predicting strain energies, molecular geometries, dipole moments, enthalpies of reaction and the like[169]. Moreover, these calculations have been extended to the 'hypothetical' cyclopropyne[170] the singlet state of which is the predicted transition state structure for the degenerate rearrangement of $CH_2{=}C{=}C{:}$; the corresponding triplet is a minimum on the C_3H_2 hyperfine surface.

The dipole moment of cyclopropene, measured[171] as 0.454 D, is well reproduced by theory[172]. However, the direction of the dipole obtained by calculation opposes that deduced from experiments. The fact that 1-methylcyclopropene has a larger[171] and the 3,3-dimethyl derivative a smaller[172] dipole moment than the parent molecule supports[172] the calculated sign with the double bond at the positive end of the dipole.

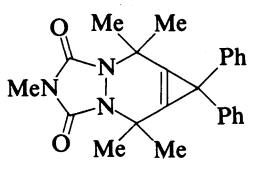
The salient features of the infrared and Raman spectra of cyclopropene and its derivatives have been discussed[9]. As mentioned above the 'double bond stretching vibration' occurs at 1641 cm^{-1}, but this medium intensity band has a considerable component of ring vibration associated with it; it is both infrared and Raman active. The replacement of H(1) by a methyl group shifts this band to 1740 cm^{-1} and by a further 150 cm^{-1} to 1885 cm^{-1} in the 1,2-dimethyl derivative. In the 3-methyl and 3,3-dimethyl analogues there is little change from the cyclopropene position. By comparison, deuterium substitution at C(1) and C(2) shifts the band to 1578 and 1525 cm^{-1} respectively. Undoubtedly[9] the coupling of the skeletal vibrations with the vibrations of the bonds to the substituents is most pronounced in the cyclopropenes. Because of the enhanced (ca. 43 %) s character of the cyclopropene C–H bonds, the vinylic C–H vibrations occur at higher (3115 cm^{-1}) wavenumber than those for cyclohexene (3045 cm^{-1}). Normal coordinate analyses of the infrared and Raman spectra of cyclopropene and its deuteriated

derivatives[109, 173], 3,3-difluorocyclopropene and its d-1 and d-2 analogues[174], tetrachlorocyclopropene[175], and the nuclear quadrupole resonance spectrum of the last[176], have been studied and various thermodynamic properties calculated[177] from the spectral data.

The electronic spectra of cyclopropenes are analogous to those of less strained analogues and conjugation of the double bond leads to the usual bathochromic shifts. As is evidenced by the cycloproparenes[93], excessive strain in the σ framework has little effect upon the electronic transitions. The photoelectron spectrum of cyclopropene[178] has been recorded and the results subjected to theoretical scrutiny[179]. The first ionization potential (9.82 eV) corresponds to ionization from the π molecular orbital. Seven valence state bands are predicted and each is observed. Bands at 10.9 and 12.7 eV (3b, and 6a, respectively) correspond to the 3e' bands of cyclopropane and the splitting of these σ molecular orbitals by 1.8 eV is not unusual. With the 3,3-dimethyl and diphenyl derivatives[180] the substituents participate in through-bond interaction with the σ orbitals of the ring and in through-space interaction with the π bond. The methyl derivatives have a HOMO localized largely in the ring whereas there is appreciable contribution from the aromatic rings in the phenyl derivatives.

The nuclear magnetic resonance (NMR) spectra of cyclopropene reflect the unusual bonding present in the ring system[9]. The vinylic protons resonate at 7.01 ppm, a value ~ 1 ppm to lower field than other cycloalkenes. This deshielding reflects the enhanced s character in the CH bond and the magnetic anisotropy of the ring bonds. The methylene protons appear at 0.92 ppm by an effect analogous to that observed for cyclopropane (Chapter 3). In the ^{13}C-NMR spectrum[9, 181] the vinylic carbons resonate at 108.7 ppm and C(3) at 2.3 ppm. The one-bond CH couplings are 228.2 and 167.0 Hz respectively. By comparison with cyclobutene C(1) and C(3) of cyclopropene are shielded by 28.5 and 29.1 ppm respectively which parallels the observed effect in the cyclopropane/cyclobutane pair (Chapter 3). The increased magnitude of the vinylic CH coupling over its counterpart in cyclobutene (170 Hz) indicates ca. 44 %s character in the bond. The substituent effects of methyl groups[181] follow the expected trends with an α-effect at C(1) or C(3) of + 7.8 ppm. The β-effect for a methyl group at C(1) is − 9.9 ppm at C(2) and + 3.9 ppm at C(3); with the substituent at C(3) the β-effect on C(1) is + 8.7 ppm. The ^{13}C-NMR spectra of polymethyl cyclopropenes have been recorded[182] and substituent parameters determined[183, 184] for various cyclopropenes[93] (see Chapter 24).

Structural data exist[166, 185] for a large number of cyclopropenes as mentioned above. The effects of substituents upon the ring bond lengths are similar to those observed for the cyclopropanes and these have been the subject of a theoretical study[186] particularly for the halogenated cyclopropanes and cyclopropenes (see Chapter 1). The ring-fused cyclopropene **30**[54] is non-planar with the three-membered ring forming an angle of 162.4° to the plane containing the six-membered ring; the carbon–carbon double bond is 128.6 pm long. By comparison the cyclopropene components of **33** are coplanar[56] with the eight-membered ring and have a double bond length of 130.2 pm. A theoretical study of the parent molecule derived from **33** at the MINDO/3 level[187] supports the planar



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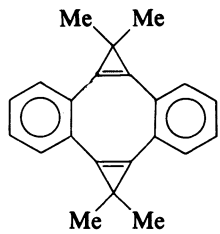
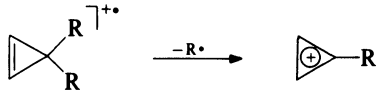


(33)

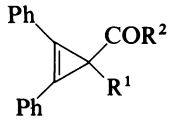
arrangement but contrasts with experiment in predicting the three-membered rings to be fused to the cyclooctatetraene single bonds. This failure of the method is compatible with the inability of MINDO/3 to predict correctly the geometry of the cyclopropareneS[93].

The intensity of the molecular ion in the mass spectrum of a cyclopropene is dependent upon the nature of the substituents at C(3) since fragmentation provides the aromatic 2π cyclopropenyl cation (equation 43). Parent cyclo-$C_3H_3^{+\cdot}$ has been generated uniquely by



(43)

such dissociative ionization[188] and characterized prior to rearrangement. The fragmentation pathways of 3-substituted 1,2-diphenylcyclopropenes **113a** lead[189] to the diphenylcyclopropenyl cation (*m/z* 191) as the base peak. The same species are generated from **113b** but less readily. Interestingly, the esters **113** (R^2 = OMe) lose Me· and not the

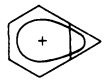


a: R^1 = H; R^2 = OMe, OH, Cl, NH_2, NMe_2
b: R^1 = OH, NMe_2; R^2 = OMe or OH

(113)

expected MeO·. The fragmentations[190] of more heavily substituted derivatives have been rationalized and appearance and ionization potentials[191] recorded.

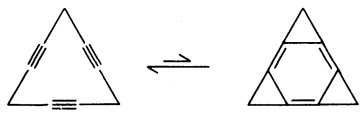
The cyclopropabenzenes fragment[93] by loss of a C(1) substituent to give the charge delocalized cyclopropabenzenyl cation, e.g. **114**. Labelling studies have shown[192] that the



(114)

carbon and hydrogen atoms of parent **114** lose their positional identity prior to further fragmentation (loss of C_2H_2). In similar vein photofragmentation spectroscopy has shown[193] that the molecular ions of allene, cyclopropene and propyne attain a common structure before fragmentation as do those from various C_4H_6 species which include 1- and 3-methylcyclopropene. The 1,1-dimethylcyclopropabenzene radical anion has been generated[194] and examined by negative ion mass spectroscopic techniques.

Finally, it should be noted that MNDO RHF calculations[195] suggest that if cyclonona-1,4,7-triyne (**115**) is to cyclize, the valence isomer **116** of tris-cyclopropabenzene (ΔH_f 947 kJ mol^{-1}) should predominate.



(115) **(116)**

IV. REACTIONS OF CYCLOPROPENES

The unusual bonding associated with the cyclopropenes resulting from the inbuilt strain gives rise to a series of molecules which are exceptionally reactive. Reactions involving each of the bond types present are known and for convenience these processes are divided into reactions involving ring retention and reactions proceeding with ring cleavage.

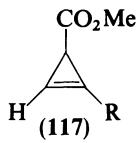
A. Reactions Proceeding with Ring Retention

As has been discussed briefly in Section III above, the ring strain of the cyclopropenes is accommodated, in part, by somewhat unusual bonding to the substituents. Structural[166] and spectroscopic[9,181] studies suggest that the vinylic C–H bonds have ca. 44% s character and that this is approximately constant in bonding to other substituents. Consequently aspects of the chemistry of the cyclopropenes are expected to reflect this with enhanced acidity of the vinylic proton. Cleavage of an exocyclic bond at C(3) will result in the cyclopropenyl cation, radical or anion with consequent interaction with the π bond and perturbation of the energy of the system. By comparison addition to the π-system to yield a cyclopropane relieves ring strain by ca. 110 kJ mol^{-1}.

1. Substitution at C(1)/C(2)

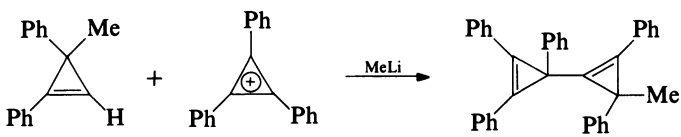
The s character of the vinylic C–H bond of cyclopropene is midway between that of sp and sp^2 hybridized bonds and some similarity in behaviour to the acetylenic C–H bond is noted[9], particularly with regard to the acidity of the proton. Molecular orbital calculations at the *ab initio* level[196] support an enhanced acidity of C(1)–H over C(3)–H in cyclopropene and correctly predict the preference for a 1-lithio derivative. A bis-lithio derivative is expected to have both lithium atoms bridging the C(1)–C(2) σ bond.

The acidity of the vinylic C–H bond[9] is exemplified[197] by the hydroxide ion-induced H/D exchange of ester **117** in competition with ester hydrolysis. Synthetically useful



(117)

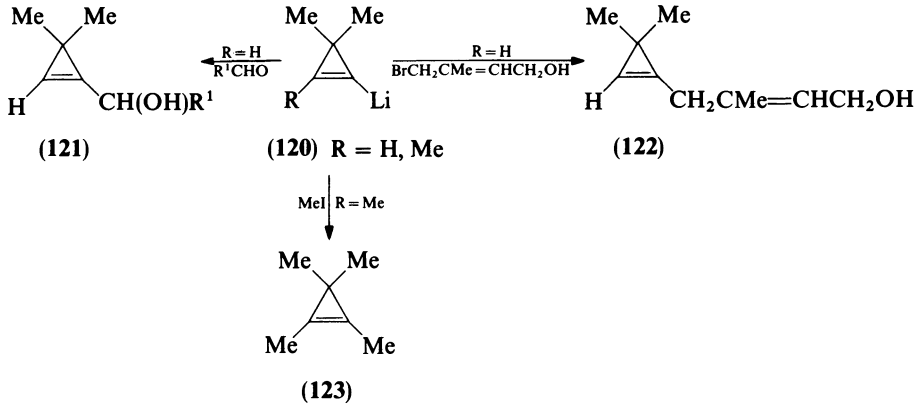
reactions involve the C(1)-lithiation of cyclopropenes and whilst this can be achieved by reaction of a 1-halo derivative with *n*-butyl lithium[84], the direct replacement of C(1)–H is well known[69,198–200]. For example, lithiation (methyl lithium) of **118** followed by reaction with triphenylcyclopropenyl perchlorate gives the 1,3′-bicyclopropenyl (**119**) in



(118) **(119)**

89% yield[69]. Reaction of organolithium **120** provides a simple route to the functionalized derivatives **121**–**123**[198,199].

The replacement of the chloro substituents of 1,2-dichloro-3,3-difluorocyclopropene by nucleophiles is known[201–203]. Thus reactions with di-isopropylamine or methoxide ion result in mono replacement of the C(1)-substituent presumably by a nucleophilic



(121) (120) R = H, Me (122)

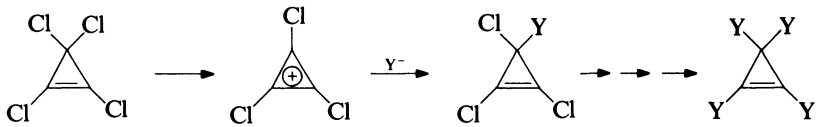
(123)

addition–elimination sequence; with potassium thiocyanate both chlorine atoms are replaced. With sodium trimethoxyborohydride the iodo substituent of 1-chloro-3,3-difluoro-2-iodocyclopropene is selectively reduced[204] in accord with the soft acid principle.

The synthesis of 1-substituted cyclopropenes from tetrahalocyclopropenes by Friedel–Crafts and related reactions involving trihalocyclopropenium ions have already been discussed (Sections II.E and II.F).

2. *Substitution at C(3)*

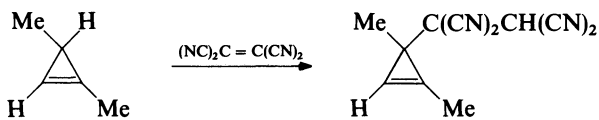
The majority of simple substitutions at C(3) of a cyclopropene[205-211] involve initial ionization and subsequent nucleophilic capture of cyclopropenyl cation. For example, tetrachlorocyclopropene is converted into its trichloro-3-fluoro analogue[205] by reaction with silver fluoride. In this way the 3-chloro substituent has been replaced by azide[206], triphenylphosphine[207] and *p*-dimethylaminopyridine[208] as well as by sulphur[209] and some carbon nucleophiles[210] (equation 44) although the reaction does not necessarily



(44)

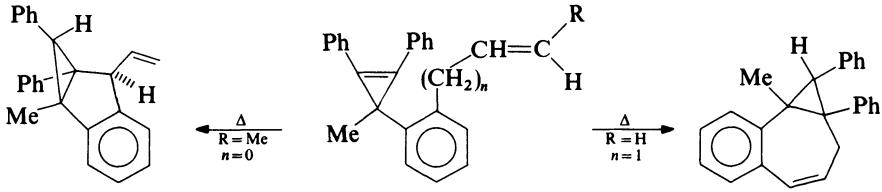
terminate at the mono replacement stage. More recently[211] 3-fluorocyclopropene has been generated from reaction of the 3-chloro analogue (available by reduction of *c*-C_3Cl_4) with rigorously dry AgF_2/KF, but the product molecule is too reactive for use in most chemistry.

For cyclopropenes which carry a hydrogen atom at C(3), the intermolecular ene reaction occurs as illustrated[212] by equation 45 with transfer of hydrogen from the cyclopropene. In the absence of a C(3)–H moiety [$_\pi 2 + _\pi 2$]cycloaddition ensues (Section IV.A.6.b). By

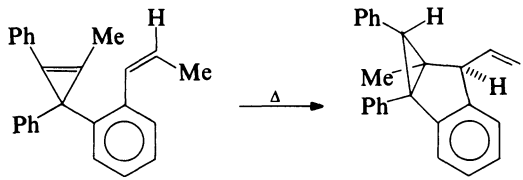


(45)

contrast the 3-arylcyclopropenes **124** provide[213] intramolecular ene products quantitatively upon themolysis by H transfer to the three-membered ring. Moreover, the reaction of unsymmetrical **125** is regiospecific in that **126** is obtained in 98% yield.

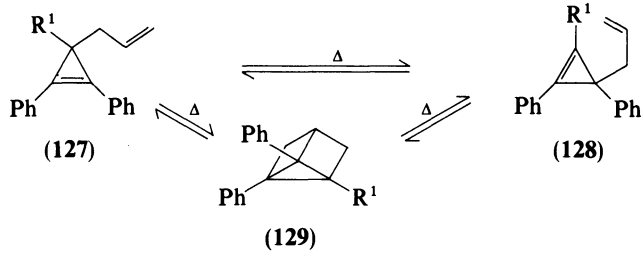


(124) $n = 0$ or 1



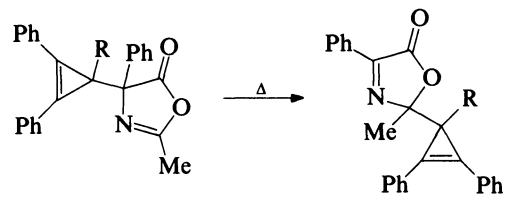
(125) **(126)** 98%

3-Allylcyclopropenes undergo thermal Cope rearrangement[214] and the bonding reorganization gives an apparent substituent migration (equation 46). Thus thermolysis of



(46)

either **127** or **128** leads to the same equilibrium mixture. Detailed studies[214] have shown that the [2 + 2]cycloadduct **129** is formed in competition with the Cope rearrangement product. An analogous process occurs with the heterocycle **130** but in this instance[215] the

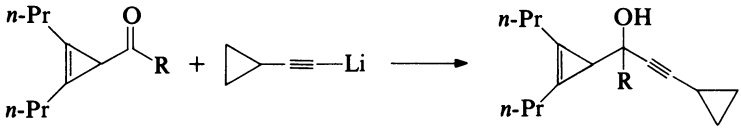


(130) R = Ph or Me

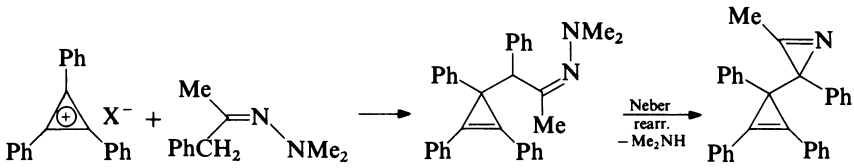
reaction involves heterolysis of the C(3)-heterocycle bond and nucleophilic capture of the cyclopropenyl cation thus formed. The overall reaction is formally a [1,3] shift of the cyclopropenyl moiety.

3. *Functionalization remote from the ring*

Much chemistry can be performed with molecules containing a cyclopropene ring whilst leaving the three-membered ring unaffected. Although a detailed discussion of such functionalization remote from the ring is beyond the scope of the current contribution, the three examples shown below serve to illustrate the possibilities:



Ref. 76



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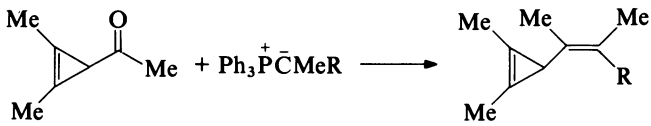
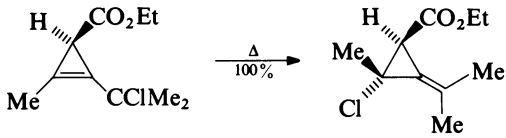


Ref. 217

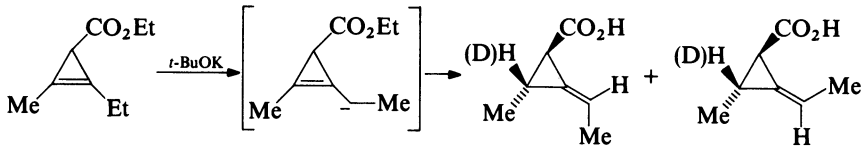
4. *Cyclopropene–methylenecyclopropane rearrangements*

Cyclopropenes with a side-chain halogen substituent located α to the double bond undergo thermal rearrangement[37] to methylenecyclopropanes as illustrated by equation 47. The reaction shows stereospecificity since the migrating group (Cl) and the



(47)

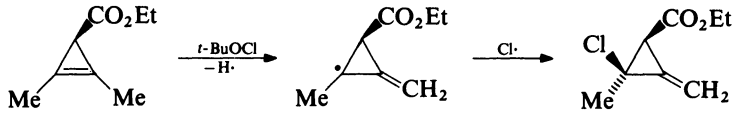
C(3) ester are always located on opposite faces of the ring. More commonly[199,218] the rearrangement is effected by base whereupon alkylcyclopropenes rearrange (equation 48). Studies have shown[218] that base abstraction of the allylic (side-chain) proton leads to the



(*E*)-major (*Z*)-minor (48)

(*E*)-alkylidenecyclopropane stereoselectively. Although proton transfer is an intermolecular process it occurs regio- and stereospecifically as shown for deuterium-labelled substrate (equation 48).

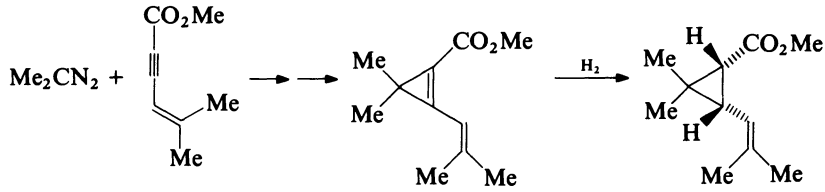
Under radical chlorination conditions at low temperature **131** is converted[219] quantitatively to **132** via the allylic radical.



(131) **(132)**

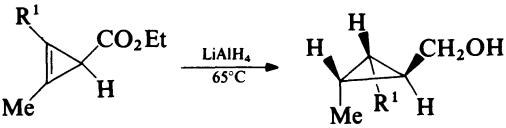
5. Simple additions to the double bond

The *cis*-hydrogenation of cyclopropenes is unexceptional in itself[9,74], but when preceded by the addition of diazopropane to the yne component of an enyne (Section II.B) it provides[53,65] a stereospecific synthesis of chrysanthemic acid esters (natural pesticides) in high yield. Reduction of unsymmetrical cyclopropenes with lithium aluminium



90%

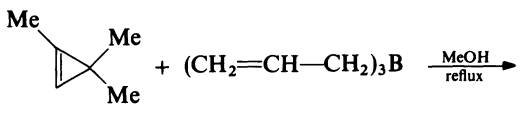
hydride[220] is regioselective since the more stable cyclopropyl carbanion is produced upon hydride transfer. With the functionalized cyclopropenes **133** the ester moiety is reduced at 0°C but the double bond is unaffected. However, at 65°C both the ester and unsaturated

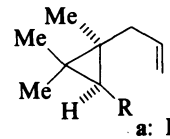


(133)

R^1 = Et, *i*-Pr, *t*-Bu

linkage are reduced, the latter in a stereospecific fashion since the aluminium atom coordinates with the oxygen of the C(3) alcohol substituent. Stereospecific *cis*-addition also



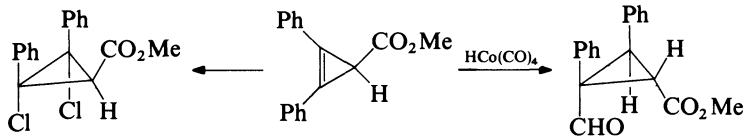


(134) **a**: R = $B(OMe)_2$ (56%)
b: R = OH (68%)

+ $Me_2CHCMe{=}CHCH_2CH{=}CH_2$
21%

occurs[221] for organoboranes but competitive ring cleavage to a 1,4-diene is problematical; alkaline peroxide cleavage of the organoborane product **134a** gives alcohol **134b** in 68% yield.

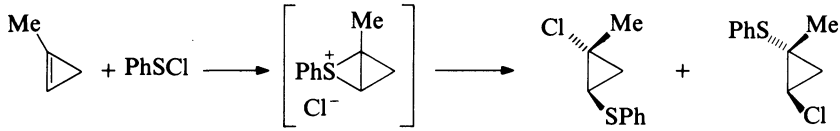
Chlorination of cyclopropenes is best effected under radical conditions due to the greater stability of the cyclopropyl radical over its cation equivalent. Thus chlorination of **135** is stereospecifically *cis* irrespective[222] of the reaction conditions but the radical path is most efficient. Radical hydrogenation and hydroformylation of cyclopropenes is effected[223] with $HMn(CO)_5$ and $HCo(CO)_4$. Intermediate caged radical pairs are



(135)

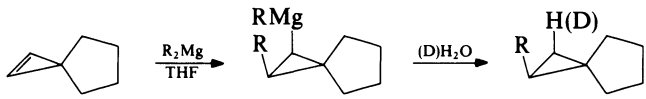
involved. Recombination within the cage leads to hydroformylation and escape from the cage results in hydrogenation. Steric factors not only influence the rate of reaction but also control the stereochemistry of the products.

Ionic additions which transform cyclopropenes into cyclopropanes are well known. The electrophilic addition of sulphenyl halides[224] proceeds by a two-step mechanism to give *trans*-disubstituted products but with little regioselectivity. Cyclic sulphonium ion intermediates are probably involved as illustrated for 1-methylcyclopropene. Electrophilic



bromination of 3,3-dimethylcyclopropene gives *trans*-1,2-dibromide[225]. Oxymercuration of cyclopropenes usually leads to products of ring cleavage but ring retention is known[226].

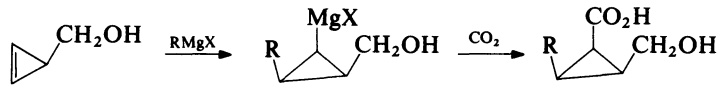
Grignard reagents add to the double bond of a cyclopropene to give a stereospecifically *cis* product[227–229] in a reaction that is common to strained double bonds. The reactions are first order in both alkene and Grignard reagent and the addition is relatively insensitive to steric bulk (equation 49). The kinetic data support product formation by a polar four



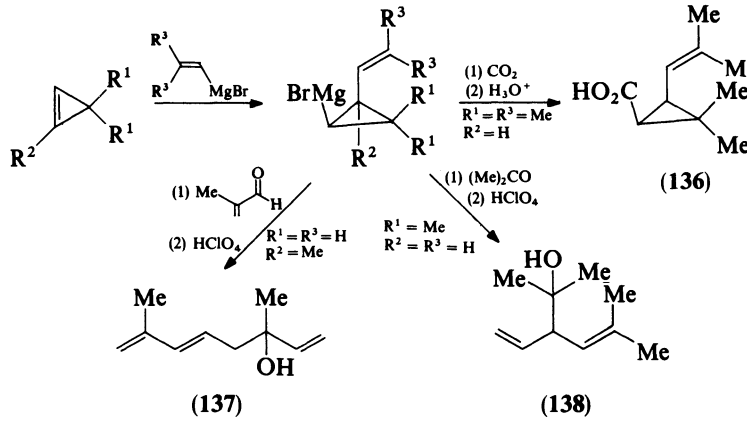
(49)

R	Me	Et	*i*-Pr	*t*-Bu
k_{rel}	1	10.3	32	8

centre transition state structure. The synthetic utility of such processes stems from the fact[227–229] that the organomagnesium product is carboxylated stereospecifically *syn* and it thus provides a facile route to *cis*-cyclopropanecarboxylic acids. A 3-hydroxymethyl substituent directs the incoming reagent stereospecifically *cis* by coordination with the reagent (equation 50)[227] and the new C–C bond is formed regioselectively at the more substituted double bond carbon atom. The reaction has been used extensively[228], provides[229] *cis*-chrysanthemic acid (**136**) stereospecifically in good yield (equation 51),



(50)

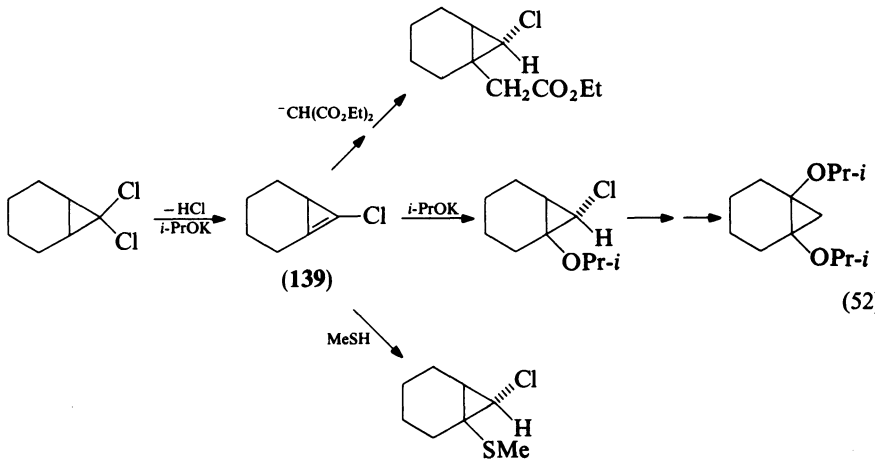


(51)

(137) (138)

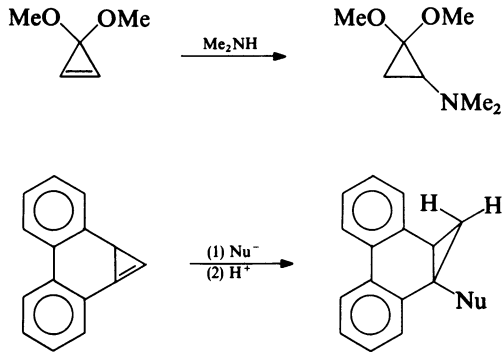
and coupled with cyclopropyl–allyl ring opening provides[230] a route to (±)-hotrienol (**137**) and (±)-santolina alcohol (**138**).

Nucleophilic additions to the cyclopropene double bond are particularly well documented for strained and/or highly reactive derivatives[80, 81, 84, 85, 144–147, 231]. Thus bicyclo-[4.1.0]hept-1(7)-ene (**139**) can be trapped[231] by oxygen, sulphur and carbon nucleophiles (equation 52) and the rapid reactions effect a *syn*-addition. Cyclopropenone dimethyl



(52)

acetal reacts with secondary amines and the strained cyclopropa[*l*]phenanthrenes (**140**) can be captured by oxygen, sulphur and selenium nucleophiles.



(140)

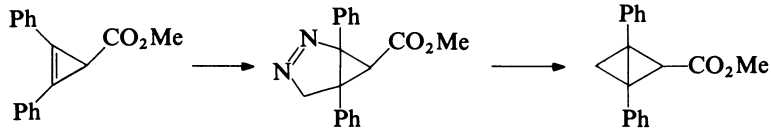
Nu = OBu-*t*, SMe, SeMe

6. Cycloaddition reactions

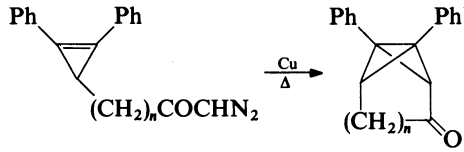
Whilst the use of cyclopropenes as dienophiles in the Diels–Alder reaction is best known, the ring participates in a wide range of cycloaddition processes.

a. [2+1] *Cycloadditions*

The intermolecular addition of a carbene to a cyclopropene to give a bicyclo-[1.1.0]butane is not a viable synthetic method since products of ring cleavage are usually observed[232]. However, diazoalkane addition to a cyclopropene (or bis-addition to an alkyne) is known to occur[123,233] and subsequent deazetation generally leads to bicyclobutane and diene by separate pathways.

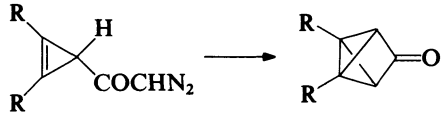


Successful [2+1] additions with the cyclopropene double bond result from intramolecular processes. For example, copper-catalysed deazetation of **141** provides[234] tricyclic product in ca. 50% yield. Analogous approaches have led[235] to the lower



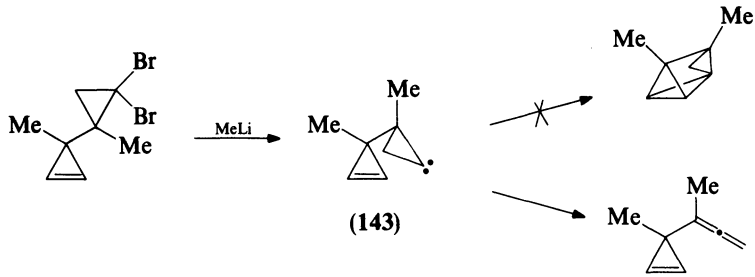
(141) $n = 1$ or 2

homologue **142a** and by dirhodium tetraacetate catalysis[47] to **142b** in 30% yield. However, by employing the bis-trimethylsilylcyclopropene, the parent ketone **142d** has been obtained[236] as a moderately stable compound but in low yield. Whilst the carbene centre of **143** is also β to the cyclopropene, the intramolecular [2+1] addition is foiled by



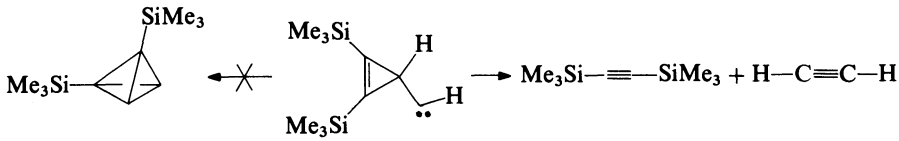
(142)

a: R = Ph
b: R = CH_2OAc
c: R = $SiMe_3$
d: R = H



(143)

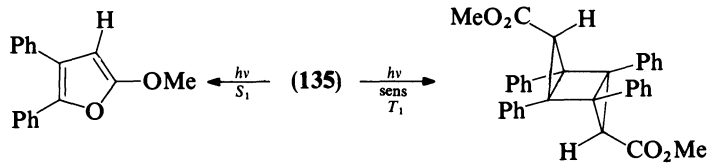
the facility of the cyclopropylidene–allene rearrangement[237]. Cyclopropenylcarbene **144** generated and trapped in a matrix at 15 K decomposes to alkynes and does not[238] cycloadd to give the tetrahedrane.



(144)

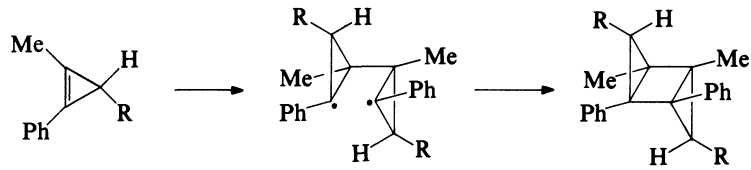
b. [2+2] *Cycloadditions*

The singlet excited state photochemistry of cyclopropenes is dominated by ring cleavage reactions (Section IV.B.2), but in the triplet manifold [2+2] cycloaddition is the major pathway. Because of inefficient intersystem crossing[239], the first excited triplet state of a cyclopropene is best populated by sensitization. Despite the added energy involved with these species there is no effective pathway available for ring cleavage; in the absence of added olefin stereospecific dimerization to a *cis*-transoid-*cis*-tricyclohexane, e.g. **145**, occurs. The smallest of the C(3) substituents is *endo* in the product[240–242]. A stepwise



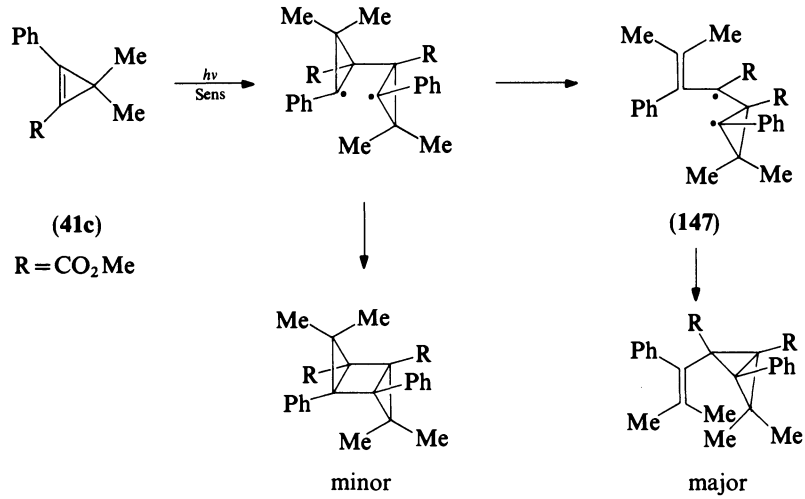
(145)

diradical mechanism[240] is consistent with the regiospecific formation of **146** from optically active substrate[241]. For isomeric cyclopropene **41c**, photodimerization leads[243] to a

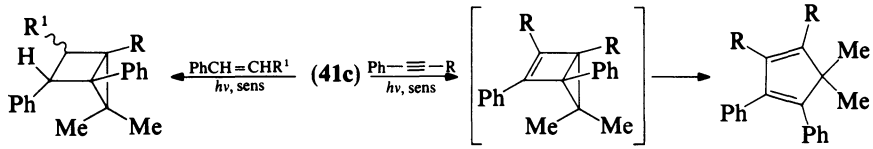


(146)

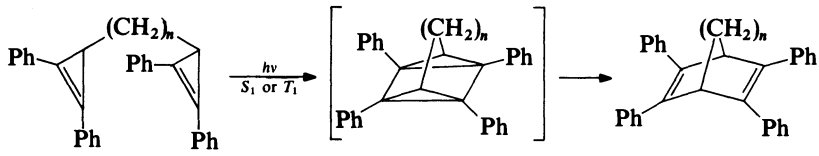
bicyclobutane as the major product of reaction probably because of the stabilization available to diradical **147** by delocalization of the cyclopropylcarbinyl radical into the ester



carbonyl group. In the presence of added olefin, however, **41c** gives products of mixed addition with a regioselectivity dictated by the stability of the intermediate diradical.

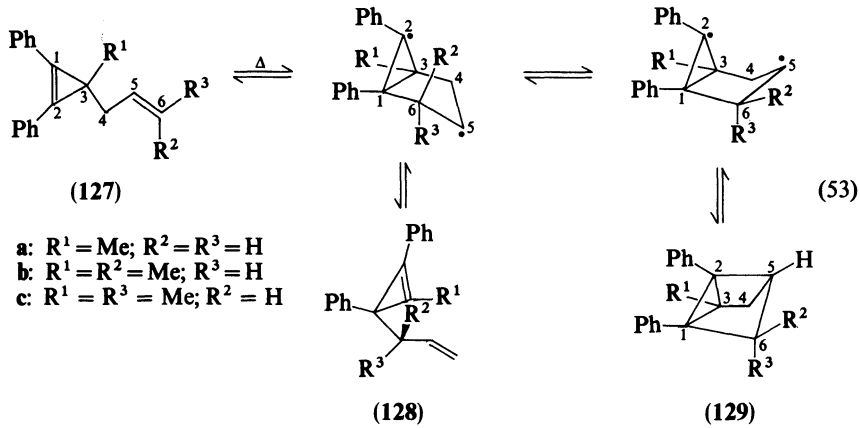


The only singlet excited state [2+2] reaction known to involve cyclopropenes is an intramolecular addition as shown below[69]:



$n = 1$ or 2

Thermal intramolecular [2 + 2] cycloadditions of 3-allylcyclopropenes, e.g. **127**, are not only known[214,244] but are also remarkably efficient (equations 46 and 53). Tricyclic products, e.g. **129**, are formed and the cycloaddition competes with stereospecific Cope

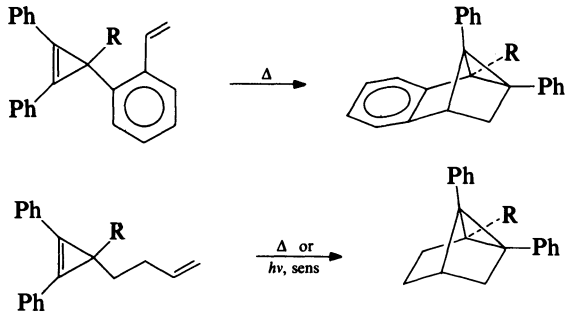


(127)

a: $R^1 = Me$; $R^2 = R^3 = H$
b: $R^1 = R^2 = Me$; $R^3 = H$
c: $R^1 = R^3 = Me$; $R^2 = H$

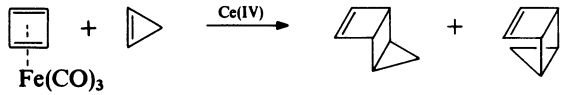
(128) (129) (53)

rearrangement (Section IV.A.2) to **128** from bifurcation of the diradical pathway (equation 53); additionally **127–129** provide the same thermal equilibrium mixture. These intramolecular [2 + 2] reactions are not restricted to allyl derivatives as illustrated below[245]. The regiospecificity observed in these cases is again consistent with formation of



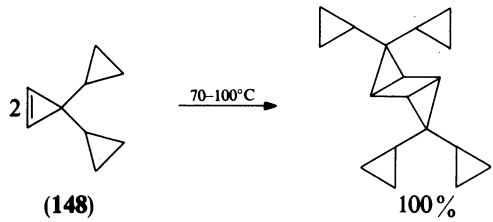
the most stabilized diradical intermediate. Interestingly, with a homoallylic side chain present the cycloaddition proceeds more cleanly upon sensitized photolysis.

Cyclopropene provides isomeric tricycles upon reaction with cyclobutadiene generated from its iron tricarbonyl complex (equation 54) but this thermal reaction is more likely to



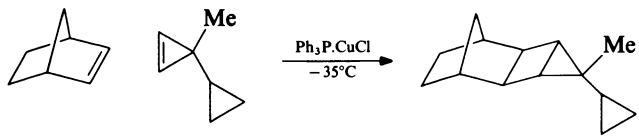
(54)

be [2 + 4] rather than a [2 + 2] process[246]. On the other hand, the quantitative formation of tricyclohexane upon mild thermolysis[77] of **148** must be a radical reaction; with boron trifluoride as catalyst the yield of product drops to 54%. Mixed additions of this type are



(148)

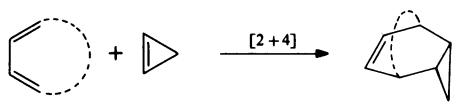
known[247] but in general the reactions, exemplified by equation 55, are more efficient under catalytic conditions.



(55)

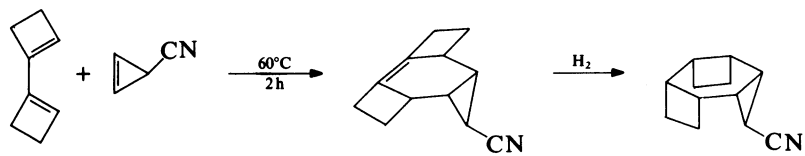
c. [2 + 4] *Cycloadditions*

With the notable exception[50a, 248] of molecules containing bulky non-electron-withdrawing substituents at C(3), cyclopropenes routinely engage in [2 + 4] Diels–Alder cycloadditions to give a bicyclo[4.1.0]hept-3-ene (**149**) or a bridged derivative



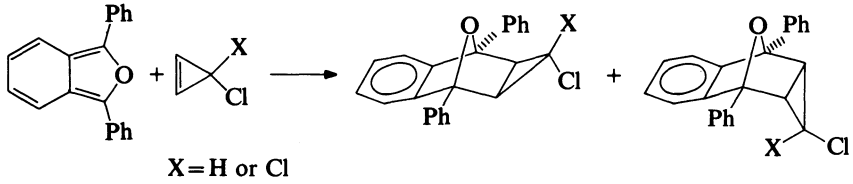
(149)

thereof[99b, 102b, 249]. For example, diene **150** and 3-cyanocyclopropene give[250] the novel tetracycle **151** (65%) as a precursor to the interesting tris-[2.2.1]-σ-homobenzene **152**.

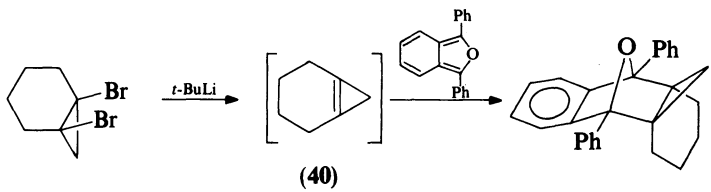


(150) (151) (152)

Most [2+4] cycloadditions of the cyclopropenes are stereoselective but they do not necessarily provide *endo* products. Whereas almost all additions to cyclopentadiene give[40,250] *endo* adducts exclusively, addition to a furan may be stereospecifically *exo*[64,251,252]. An exception to the first class of reaction lies with 3,3-difluorobis(trifluoromethyl)cyclopropene which gives[253] *exo* and *endo* adducts in a ratio of 31:69. Of the second type, the reaction of 3-chlorocyclopropene with 1,3-diphenylisobenzofuran produces[254] *exo* and *endo* adducts in a ratio of 4.5:1 whereas 3,3-dichlorocyclopropene, with a more electropositive C(3) atom, gives *exo* adduct stereospecifically. An *exo* adduct is also obtained from tetracyclone and 3-chlorocyclopropene[254].



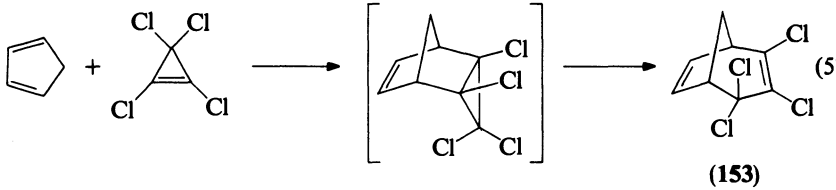
The existence of many reactive cyclopropenes incapable of isolation has been established from trapping experiments[82,87], particularly with diphenylisobenzofuran, as illustrated for the highly strained derivative **40** (equation 56).



(56)

(40)

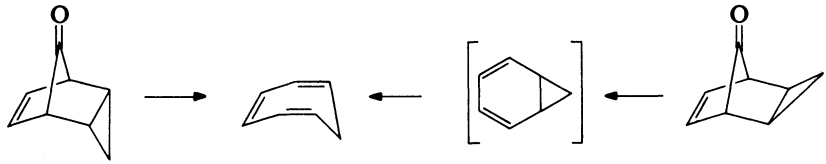
Certain of the bridged Δ^3-norcarenes depicted by **149**, and formed by [2+4] cycloaddition, rearrange to cycloheptadienes or -trienes under the reaction conditions[248]. For example, tetrachlorocyclopropene and cyclopentadiene give[255] **153** in 95% yield by facile two-electron disrotatory cyclopropyl–allyl opening of the primary [2+4] *endo* adduct (equation 57). The cycloadditions of simple cyclopropenes with dienes such as



(57)

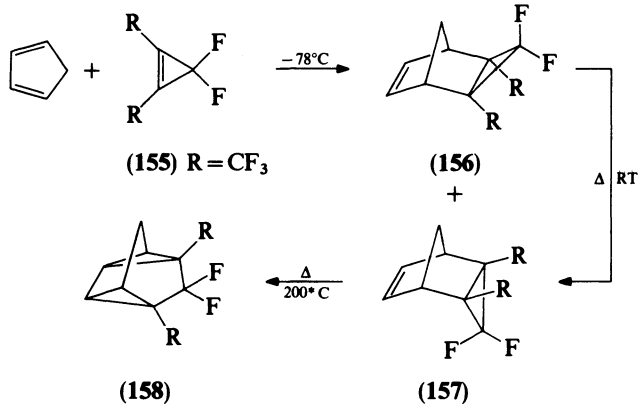
(153)

thiophene-1,1-dioxides and cyclopentadienones provide useful routes to a variety of cycloheptatrienes[256]. Here the initial *endo* cycloadduct loses[256b] sulphur dioxide or carbon monoxide cheletropically with concomitant opening of the three-membered ring. In this context **154**, the formal *endo* adduct of cyclopentadienone and cyclopropene, decarbonylates directly to cycloheptatriene at room temperature[257] in contrast to its *exo* isomer which affords the same product but by way of norcaradiene. This is expected from stereoelectronic considerations and cyclopropyl group participation.



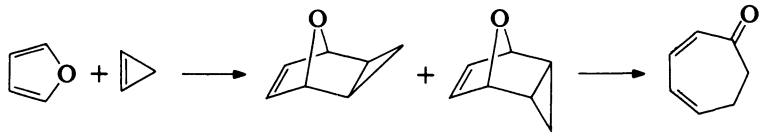
(154)

Some of the adducts derived from the addition of a cyclopropene to a cyclopentadiene cycloadd intramolecularly upon heating to afford homoquadricyclane derivatives[248, 258]. For example[253], cyclopropene (**155**) gives a ca. 1 : 2 ratio of the anticipated adducts **156** and **157** at −78°C. Quantitative rearrangement of the *exo* to the *endo* isomer occurs on warming the mixture to ambient temperature, but thermolysis of the *endo* product **157** at 200°C surprisingly provides the homoquadricyclane **158** and a diradical pathway is likely.



(155) R = CF_3 (156) + (158) (157)

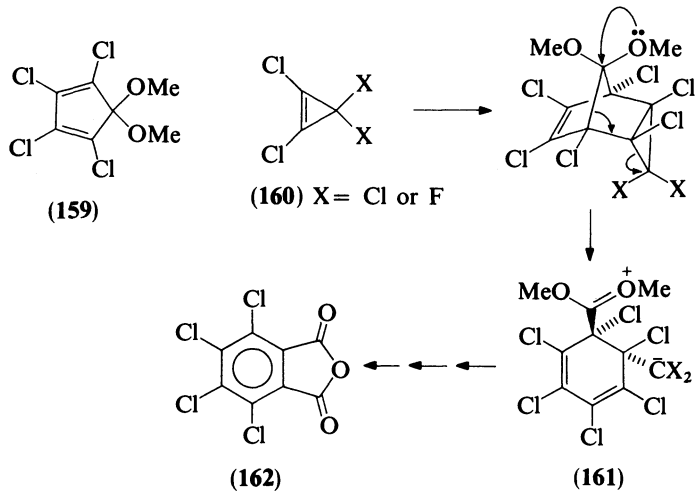
The reaction of furan with cyclopropene gives[259] both adducts but the *endo* isomer rearranges during GLC (probably at an acidic site on the surface of the injector) to give 2,3-dihydrotropone (equation 58).



(58)

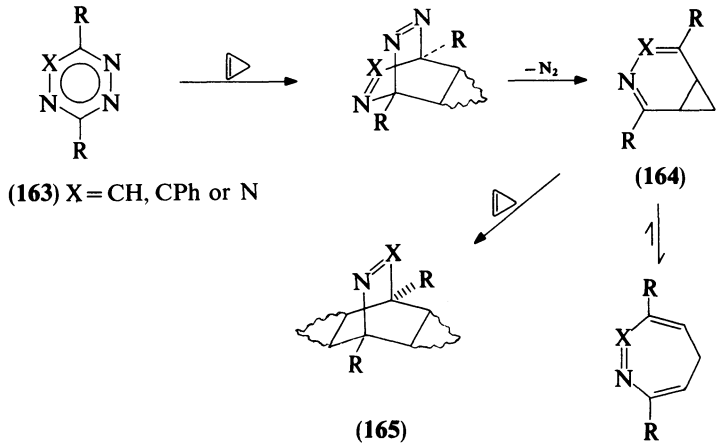
The aromatization of bridged adducts (**149**) is known. For example[255], tetrachlorophthalic anhydride (**162**) is formed in moderate yield from acetal **159** and halocyclopropenes **160**. In all probability the initial adduct spontaneously cleaves to zwitterion **161** in which the charges are stabilized (equation 59). Although its subsequent conversion into product is not fully understood, **161** has the appropriate skeleton for transformation into **162**.

Cyclopropenes react with a variety of heterodienes to give products[260] which may or may not undergo rearrangement or elimination processes. Various tris- and tetra-azines, e.g. **163**, afford products[261] which readily lose nitrogen to give azanorcaradienes, e.g. **164**.



(59)

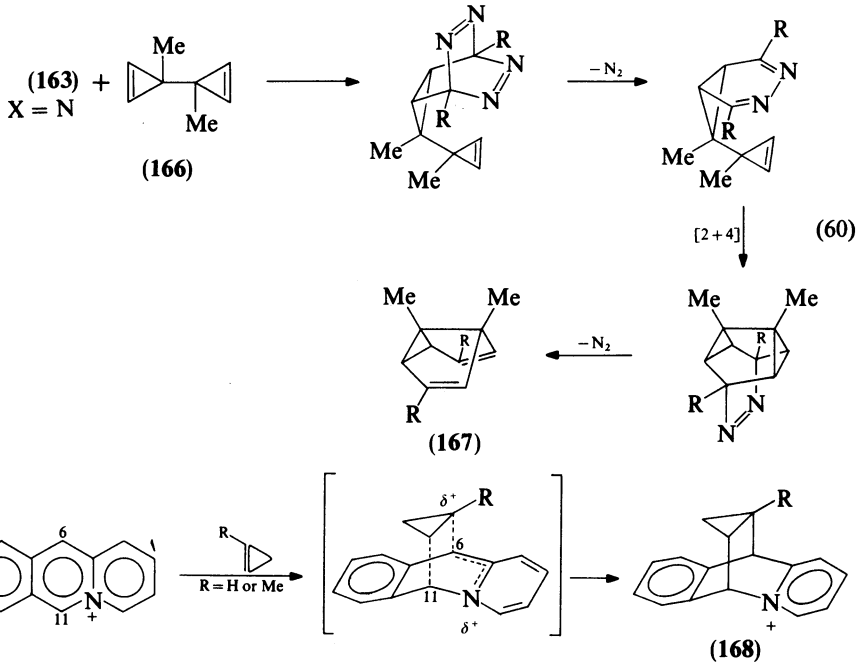
These latter compounds, particularly **164** (X = N), can engage in further $[_{\pi}2_s + _{\pi}4_s]$ cycloaddition with a second molecule of cyclopropene to give[261] a bis-adduct, e.g. **165**. For



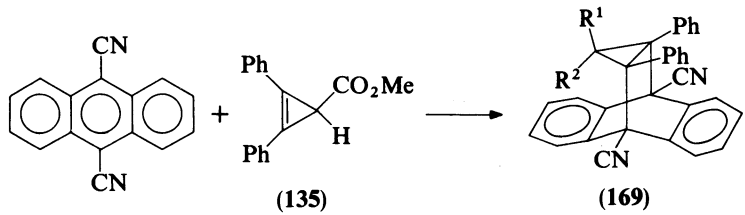
164 (X = CH or CPh) electrocyclic cleavage is more commonly observed[262]. Of such examples[93, 263, 264] the domino-Diels–Alder-like synthesis[265] of semibullvalenes deserves mention. Thus, intermolecular reaction of tetrazine **163** (X = N) with bicyclopropenyl **166** provides a labile adduct which ejects nitrogen. A subsequent intramolecular [2+4] addition and loss of nitrogen gives semibullvalene (**167**) (equation 60).

Cationic additions of cyclopropenes are illustrated[266] by the rapid and highly stereoselective addition of cyclopropene and its 1-methyl derivative to the 6,11-positions of the acridizinium cation. A marked preference (80–90%) is shown for the regioisomer **168** (R = Me) which results from electrophilic attack of the cation on 1-methylcyclopropene such that charge separation is maximized.

The addition of cyclopropene **135** across the 9,10-positions of 9,10-dicyanoanthracene is effected photochemically[267]. In non-polar solvents an emitting exciplex is generated



between singlet excited dicyanoanthracene (^{1}DCA*) and **135**. This yields the [2+4] adduct **169a** with an *exo*-ester group. In more polar media, e.g. acetonitrile, electron



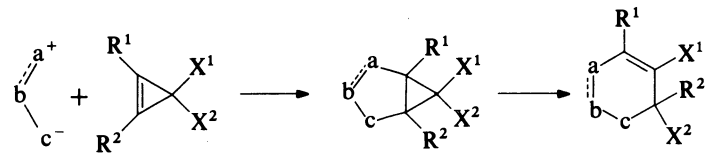
a: $R^1 = CO_2Me$; $R^2 = H$
b: $R^1 = H$; $R^2 = CO_2Me$

transfer produces radical cation $\mathbf{135}^{+\cdot}$ and radical anion $DCA^{-\cdot}$. These entities add via the radical cation tautomer to give **169b** with an *endo*-ester upon reketonization.

Cyclopropenes with bulky C_3 substituent(s) add with high stereofacial selectivity to 1,3-dienes such that *exo* rather than *endo* adducts are obtained (Y. Apeloig, personal communication, September, 1986).

d. Dipolar [2+3] cycloadditions

The cyclopropene π bond acts as a dipolarophile for a wide range[123] of 1,3-dipoles (equation 61). The initial [2+3] adduct **170** (a, b and c represent substituted atoms of C, N, and/or O) which results can expand to a six-membered heterocycle, particularly when the cyclopropene contains a good leaving group at C(3), e.g. **170** (X^2 = Cl). Less frequently ring fission in **170** gives open-chain products.

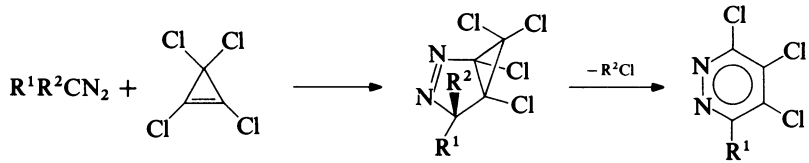


(61)

(170)

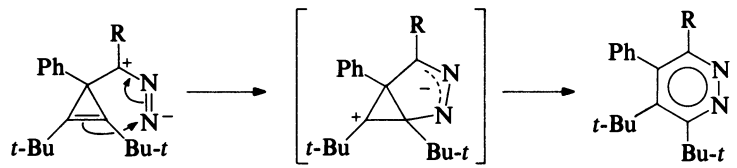
open-chain products

The synthesis of 2,3-diazabicyclo[3.1.0]hex-2-enes (**171**) is a well studied process[49, 123, 268, 269]. Whilst the addition of tetrachlorocyclopropene to diazopropane affords bicycle **171** ($R^1 = R^2 = Me$) at room temperature, analogue **171** ($R^1 = R^2 = H$)



(171) (172)

from reaction with diazomethane cannot be isolated as elimination of hydrogen chloride is much more facile than loss of methyl chloride, and pyridazine **172** is isolated[269]. In a related reaction (diazomethyl)cyclopropenes **173** yield pyridazines **175** under mild

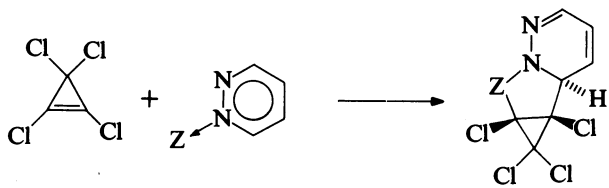


(173) (174) (175)

R = $POPh_2$, $POMe_2$, PO(OMe)Ph

conditions but betaines **174** rather than bicyclobutanes are the more likely reaction intermediates[270].

Dipolar cycloadducts **176** are available from the reactions of cyclopropenes with azomethine ylids[123], pyridinium ylids[271], aryl nitrile oxides[50a, 272–274], alkyl nitrile

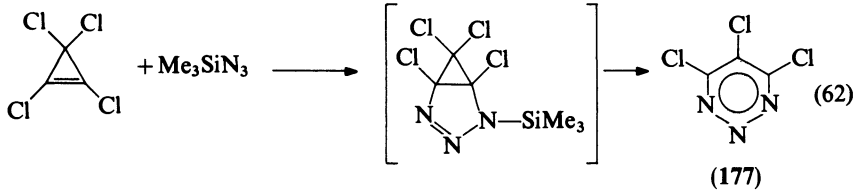


Z = NCO_2Et or $C(CN)_2$

(176)

oxides[275], imine oxides[276] and diarylnitrilimines[273]. Perhalocyclopropenes react with pyridazinium *N*-ylids to give 1 : 1 adducts as exemplified by **176** which has been subjected to structural study[277].

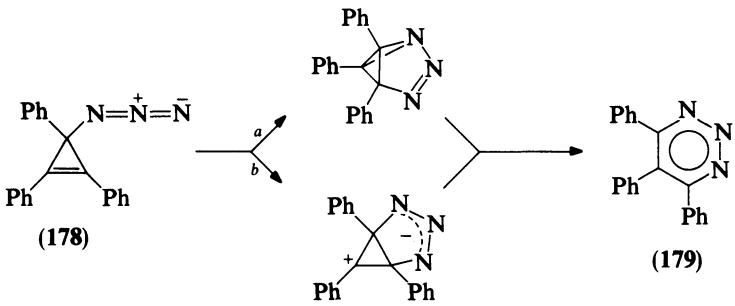
Rearrangement and elimination products of transient 1,2,3-triazabicyclo[3.1.0]hex-2-enes are isolated from the reactions of cyclopropenes with azides. For example[201], tetrachlorocyclopropene and trimethylsilyl azide afford triazine **177** from addition and subsequent loss of trimethylsilyl chloride (equation 62). Intramolecular rearrangement of



(62)

(177)

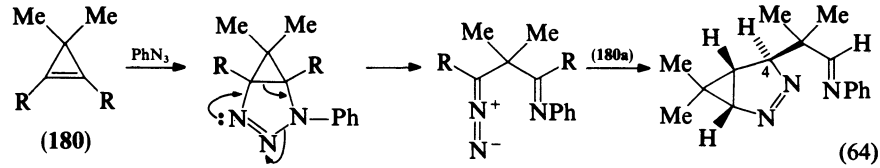
azidocyclopropene **178** to triazine **179** could involve[278] either 1,3-dipolar addition (path *a*, equation 63) or electrophilic attack on the cyclopropene double bond by the azide group (path *b*, equation 63). The reaction[268] of 3,3-dimethylcyclopropene (**180a**) with phenyl



(63)

(178) **(179)**

azide gives a 2 : 1 adduct (equation 64). Initial [2 + 3] cycloaddition can be followed by cycloreversion to **181a**. Incorporation of a second molecule of the cyclopropene will give product (equation 64) with the bulky C(4) substituent in the less hindered *exo* position.



(64)

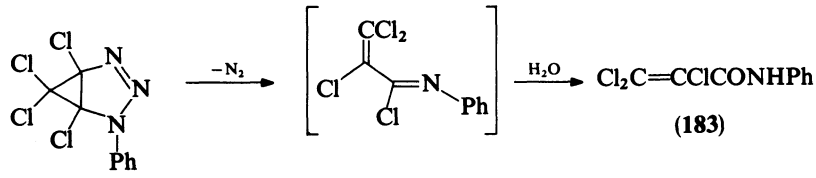
(180)

a: R = H
b: R = CO_2Me

(181)

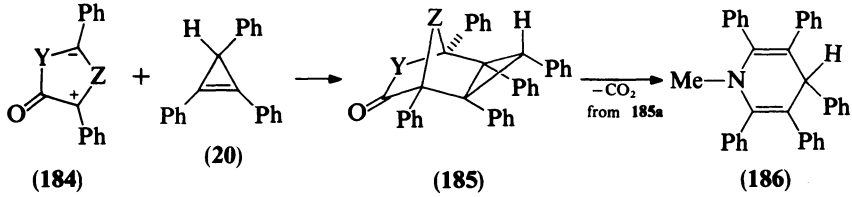
a: R = H
b: R = CO_2Me

Support for this mechanism stems from isolation of diazo compound **181b** from the analogous reaction[279] of diester **180b**. By comparison adduct **182** (from tetrachlorocyclopropene and phenyl azide) is extremely labile and gives acrylamide **183** upon nitrogen loss and hydrolysis[269].



(182) (183)

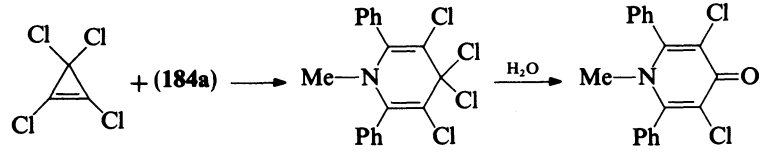
Dihydropyridines and 4-pyridones have been obtained from reaction of cyclopropenes with the oxazolium species **184a**. Thus **20** (Ar = Ph) and **184a** give the dihydropyridine **186** without isolation of the [2+3] adduct[280]. By comparison **185b**, formed[281] by



(184) (20) (185) (186)

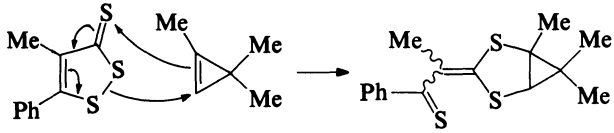
a: Y = O; Z = NMe
b: Y = S; Z = NMe

reaction with **184b**, is stable. Tetrachlorocyclopropene and dipole **184a** afford[282] pyridone **187b** since the 4,4-dichlorodihydropyridine (**187a**) hydrolyses during workup.



(187a) (187b)

4-Methyl-5-phenyl-1,2-dithiolene-3-thione cycloadds[283,284] to 1,3,3-trimethylcyclopropene. The two isomeric ketene thioacetals **188** are obtained in moderate (27%) yields.



(188)

B. Reactions Proceeding with Ring Cleavage

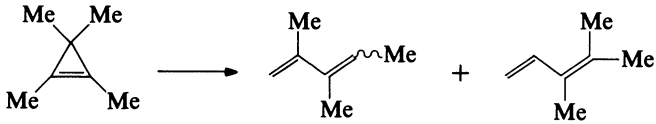
1. Thermal reactions

Because of the high strain energy[163,164,285] associated with the cyclopropenes (228 kJ mol^{-1}) thermal ring cleavage reactions are easily brought about[50b,286-290] as discussed in the following pages.

The kinetics and mechanisms of the gas phase pyrolysis of cyclopropene in the temperature range 193–243°C has been examined experimentally and theoretically[291]. The major and minor products of reaction are propyne and allene respectively; propyne results from a unimolecular isomerization with an activation energy[291] of 147.3 kJ mol^{-1}. Moreover, cyclopropene is most likely the important intermediate in the thermal isomerization of allene to propyne[291]. These observations are accommodated by the reactions of equation 65. The activation energy for the conversion of allene into cyclopropene is 269 kJ mol^{-1} and that for the reverse process is 182 kJ mol^{-1}.

$$CH_2{=}C{=}CH_2 \rightleftharpoons \triangle \rightleftharpoons CH_3{-}C{\equiv}CH \qquad (65)$$

The thermolysis of alkyl-substituted cyclopropenes gives rise to a mixture of alkynes and dienes[292], but as the number of substituents on the cyclopropene increases so does the stability. Thus, the thermal isomerization of 3-methylcyclopropene at ca. 230°C produces buta-1,3-diene and but-2-yne with an activation energy of 145 kJ mol^{-1}. By comparison the related reaction of tetramethylcyclopropene (**123**) (equation 66) affords dienes **189** and **190** less readily (E_a = 167 kJ mol^{-1}).

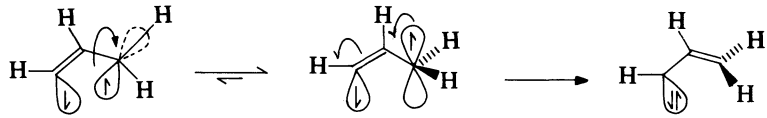


(123) (189) (190) (66)

85% *trans*
5% *cis*

10%

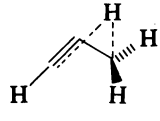
The formation of products from cyclopropene ring-opening could involve either a diradical or a vinylcarbene intermediate[291]. Generalized valence bond calculations show[293] that cyclopropene correlates through the open, non-planar diradical **191** to the singlet **192** termed 'A''. This latter species has one electron in a hybrid orbital and one in a non-bonding orbital and it is presumed[286] to decay without an activation barrier to the more stable (9.6 kJ mol^{-1}) singlet carbene **193** termed 'A'. The cleavage of cyclopropene is expected[294] to proceed by rupture of a single bond, with an overall[293] energy of 178 kJ mol^{-1} to give singlet **193** lying 153 kJ mol^{-1} above the ground state.



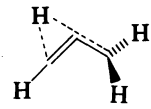
178 kJ mol^{-1} 163 kJ mol^{-1} 153 kJ mol^{-1}

(191) (192) (193)

The formation of propyne and allene by pyrolysis of cyclopropene arises from opposite [1,2]H shifts in diradicals **191** or **192**[291]. The substantially larger activation energy (by some 24.5 kJ mol^{-1}) for formation of allene reflects differences in the transition state structures for the two processes. Thus, the propyne-forming reaction requires the migrating hydrogen atom to span a single bond (see **194**), whilst in the allene-forming process a double bond is involved and a more strained situation ensues (see **195**). The formation of but-2-yne from 3-methylcyclopropene is similarly rationalized but the

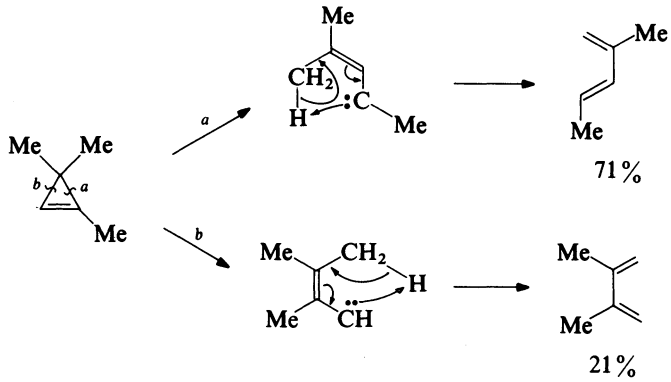


(194)



(195)

appearance of buta-1,3-diene involves C–H insertion of the carbene (see equation 67 below). With trimethylcyclopropene two modes of ring cleavage (paths *a* and *b*, equation 67) occur[292], but formation of the more highly substituted carbene by cleavage of

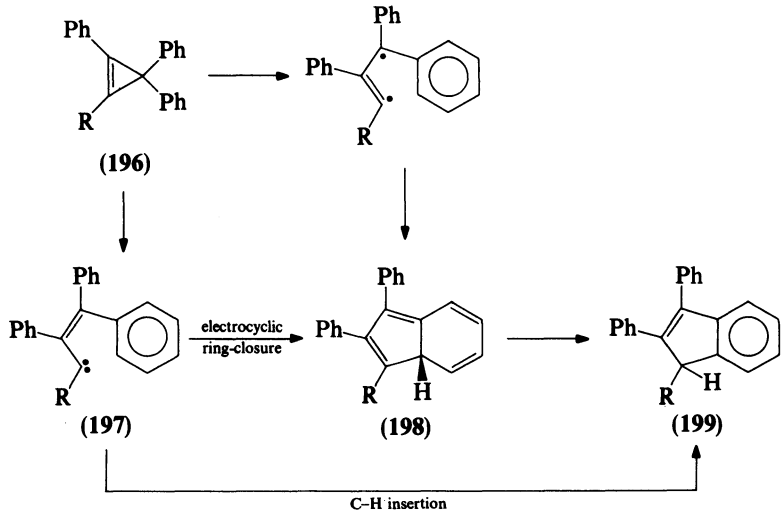


71%

21%

(67)

bond *a* is favoured. The quantitative formation of 1,2,3-triphenylindene **199a** upon thermolysis of tetraphenylcyclopropene (**196a**) probably involves[50b,287,295] carbene **197a** (rather than a diradical), which can close to **198a** or insert to give **199a** directly (equation 68). Ester **196b** behaves similarly[61,296].

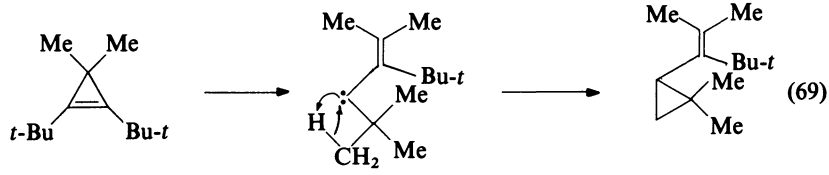


(196) (197) (198) (199)

(68)

a: R = Ph
b: R = CO_2Me

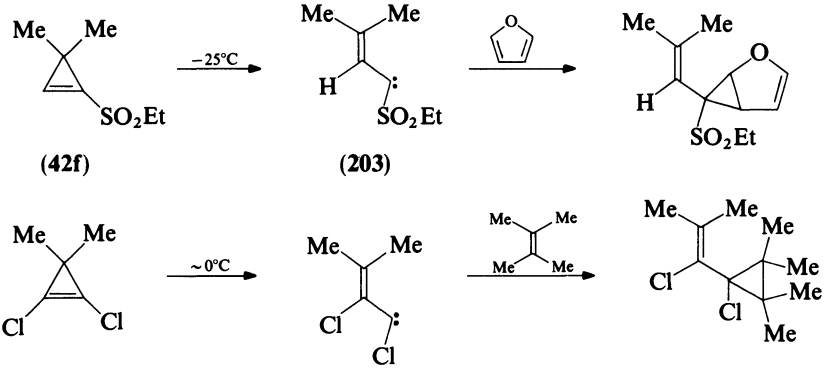
Definitive evidence for vinylcarbene intervention during cyclopropene thermolyses stems from the identification[297] of cyclopropane **202** as a primary product from cyclopropene **200** (equation 69). Product **202** can only come from an intramolecular C–H



(69)

(200) **(201)** **(202)**

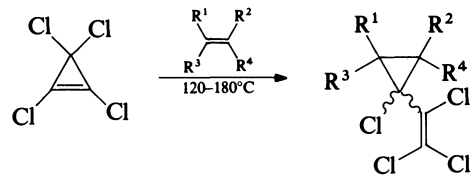
insertion reaction of carbene **201**. Moreover, cyclopropene **42f** ring-opens[68] at −25°C to carbene **203** which is readily trapped by furan whilst **42g** cleaves[86] to carbene **204** which



(42f) **(203)**

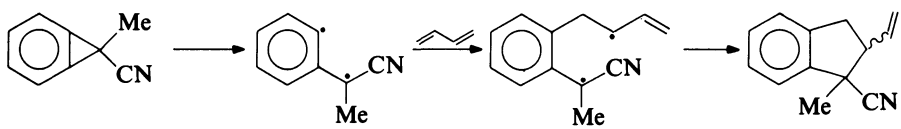
(42g) **(204)**

adds cheletropically to olefin. In a similar manner the synthetically valuable[298] vinylcyclopropanes **205** are available[299] from pyrolysis of tetrachlorocyclopropene.



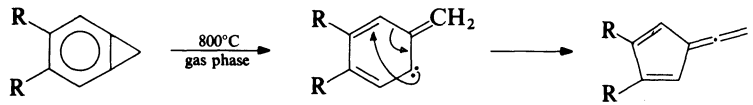
(205)

Cyclopropabenzenes exhibit dichotomous behaviour under pyrolytic conditions. Stereoisomeric indanes **207** are formed[300] from mild thermolysis of **206** in the presence of



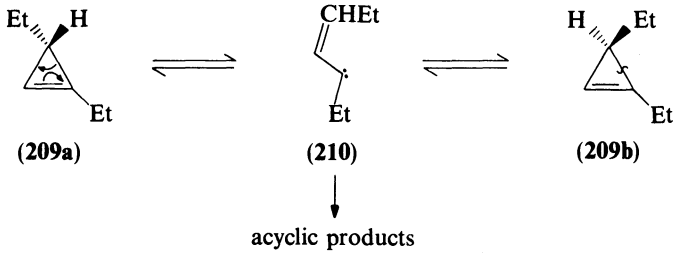
(206) **(207)**

buta-1,3-diene presumably by way of diradical intermediates. In contrast, the efficient (> 62%) formation of vinylidenecyclopentadienes (**208**) from the flash vacuum pyrolysis of the cycloproparenes is the result of a Wolff-like rearrangement of initially formed vinylcarbene[301].



R = H or RR = benzo fusion **(208)**

As discussed earlier (Section II.B) the ring closure of vinylcarbenes provides a viable and synthetically useful route to cyclopropenes. These and the above-mentioned results suggest that the cyclopropene–vinylcarbene rearrangement is a reversible process. Elegant evidence for this comes[302] from the thermolysis of optically active 1,3-diethylcyclopropene (**209**). Thus cleavage of the more substituted ring bond would give the achiral

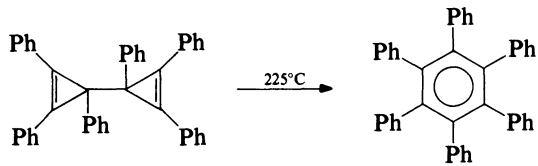


(209a) **(210)** **(209b)**

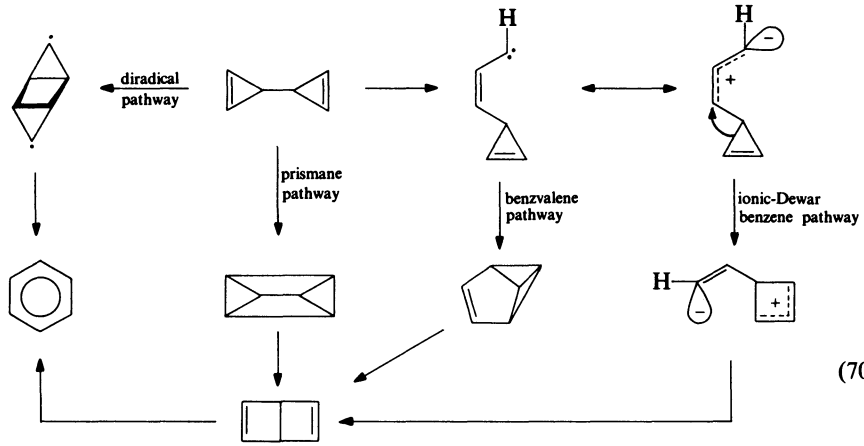
acyclic products

carbene **210**; any reclosure must then provide racemic **209** (i.e., a 1:1 mixture of **209a** and **209b**). In the event, thermolysis of **209** in the temperature range 161–190°C leads to racemization of the cyclopropene at a rate nine times faster than that for isomerization to acyclic products; the cyclopropene–vinylcarbene reaction is thus reversible. As expected no products result from cleavage of the less substituted ring bond.

The thermal rearrangements of 3,3′-bicyclopropenyls to benzene derivatives are amongst the most exothermic unimolecular processes known and these fascinating isomerization reactions have been subjected to detailed scrutiny[303–314]. The 3,3′-bicyclopropenyl is the highest energy $(CH)_6$ species[303] and the facile rearrangement is exemplified by the quantitative[304] conversion of hexaphenylbicyclopropenyl into hexaphenylbenzene at 225°C. The mechanism of such transformations has been the subject of

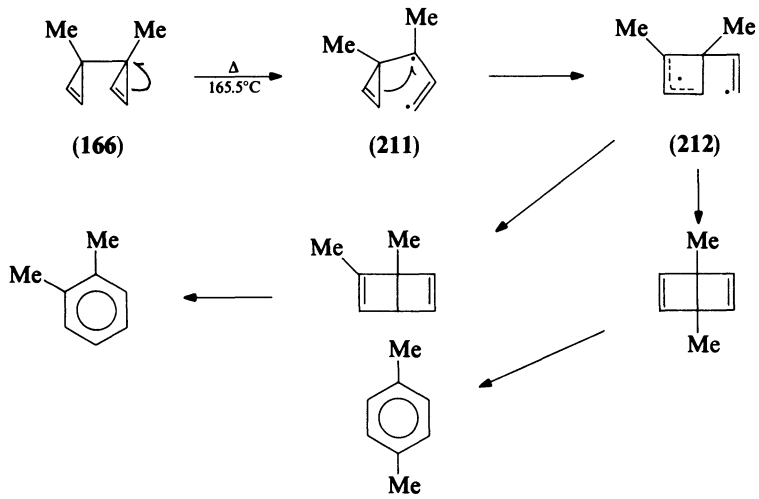


debate and at various times benzvalene[307, 308], prismane[309], diradical[311] and Dewar benzene[312] intermediates, as well as an ionic pathway[312], have been proposed (equation 70). Definitive experiments on the gas-phase pyrolysis of 3,3′-dimethylbicyclopropenyl (**166**), and related compounds, have now permitted a distinction to be made between



(70)

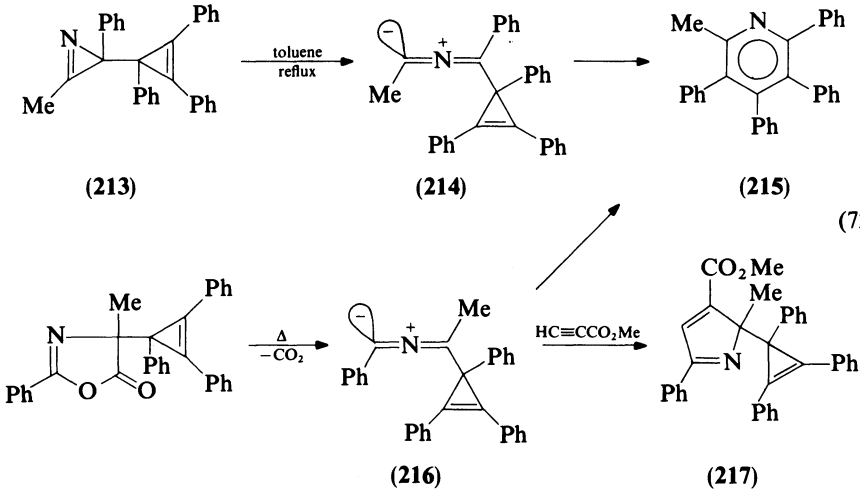
these various possibilities. The formation of *o*- and *p*-xylene from pyrolysis of **166** is best[313, 314] accounted for by the mechanism shown in equation 71. Thus, conversion of



(71)

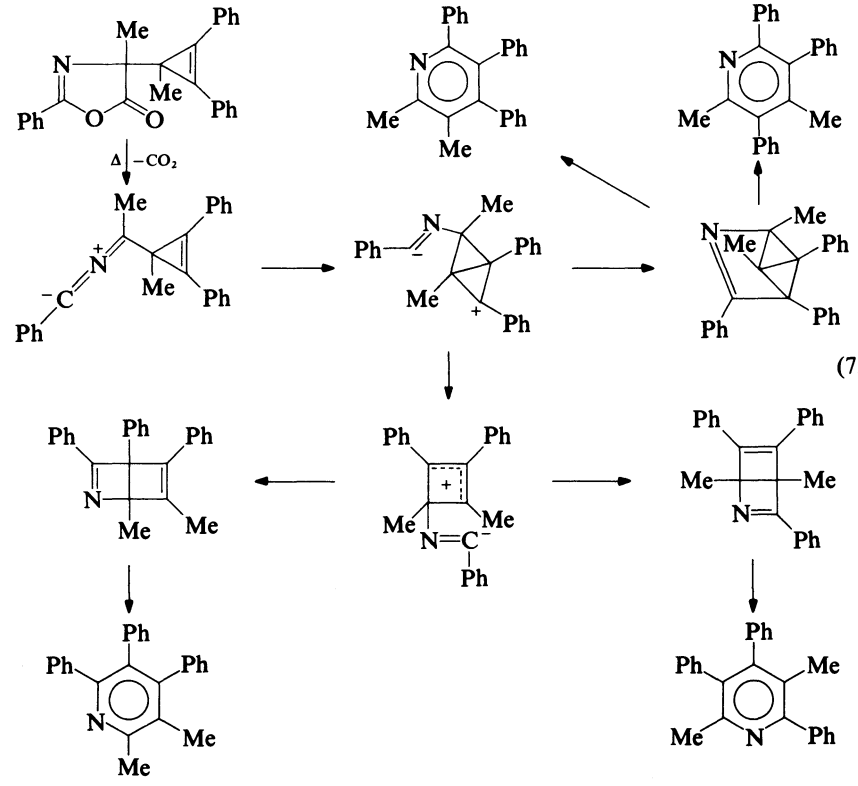
166 into diradical **211** is followed by ring expansion to the cyclobutenyl diradical **212**. The Dewar benzenes resulting from radical closure aromatize to give the observed xylenes. Chemiluminescence, which is known to be associated with the aromization of Dewar benzenes, but not of benzvalenes or prismanes, is observed[314] when the reaction is conducted in the liquid phase.

3-Azirinylcyclopropenes, e.g. **213**, are converted quantitatively into the corresponding pyridine derivatives, e.g. **215**, on pyrolysis (or photolysis) via nitrile ylides, e.g. **214**[216]. The independently generated isomer **216** (equation 72) gives the same pyridine and can be diverted to adduct **217** in the presence of dipolarophile. Insights into the detailed sequence of events involved in the conversion of ylids such as **214** and **216** into pyridine have been



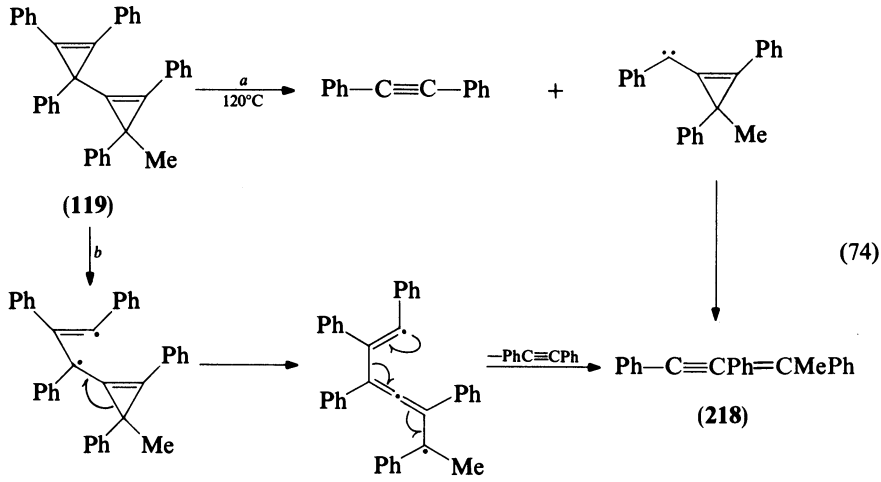
(72)

gained from product distribution studies involving more extensively labelled ylid precursors as illustrated by equation 73[216].



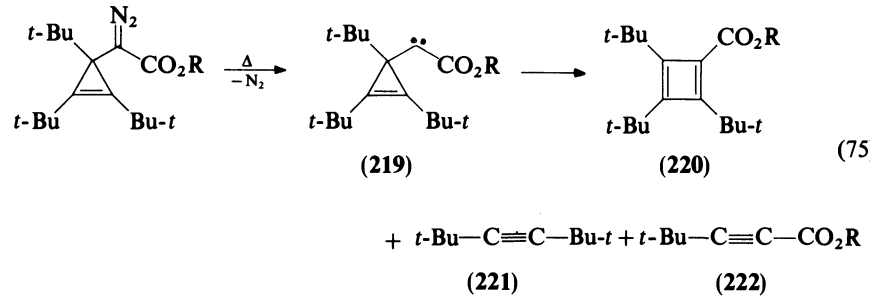
(73)

The 1,3′-bicyclopropenyl **119** affords a mixture of diphenylacetylene and enynes **218** on thermolysis (equation 74)[315]. Two pathways can account for the products. Path *a* involves



(74)

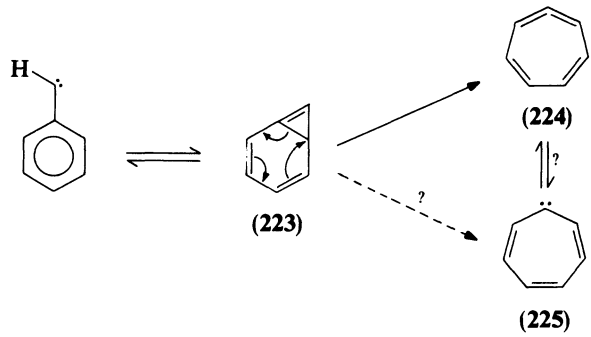
cheletropic ejection of carbene from **119** and rearrangement of it to the enynes **218**, whilst path *b* requires a homolytic fission. However, cyclobutadiene **220** and alkynes **221** and **222** are formed[316] from carbene **219** (equation 75). The absence of comparable products



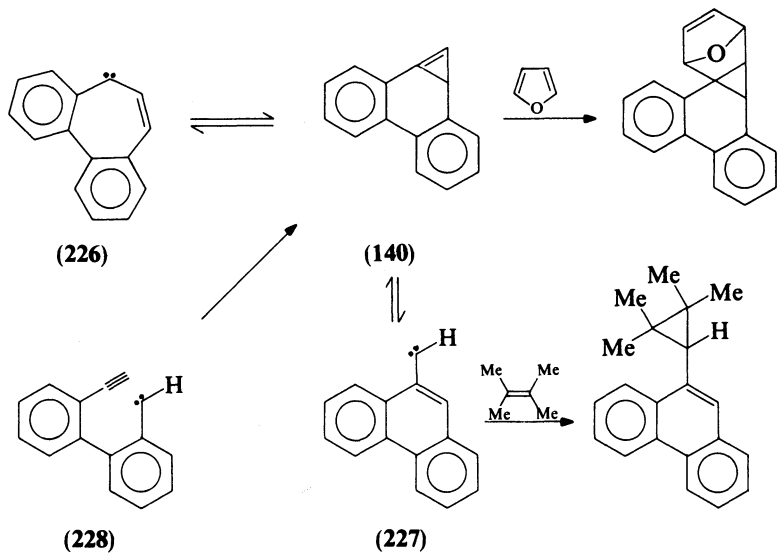
(75)

from intramolecular insertion in the reaction of bicyclopropenyl **119** is taken[315] as evidence against the carbene path (path *a*, equation 74) and the diradical mechanism is assumed to operate.

Bicyclo[4.1.0]heptatrienes, e.g. **223**, are generally accepted[288–290] as intermediates in the interconversion of arylcarbenes to cycloheptatrienylidenes, e.g. **225**. MINDO/3 calculations predict an activation energy of 26.4 kJ mol^{-1} for rearrangement of the singlet carbene into **223** whereas rearrangement of the triplet carbene bypasses **223** and gives **225** with an expected activation energy of 110.9 kJ mol^{-1}. Until recently, it was assumed that the **223** → **225** conversion proceeded by a simple ring cleavage. However, theoretical[317] and experimental[288] evidence now suggests that cycloheptatetraene (**224**) is of lower energy than the planar carbene **225** and that conversion proceeds by electrocyclic opening of **223**, the norcaradiene form of cycloheptatetraene (**224**).

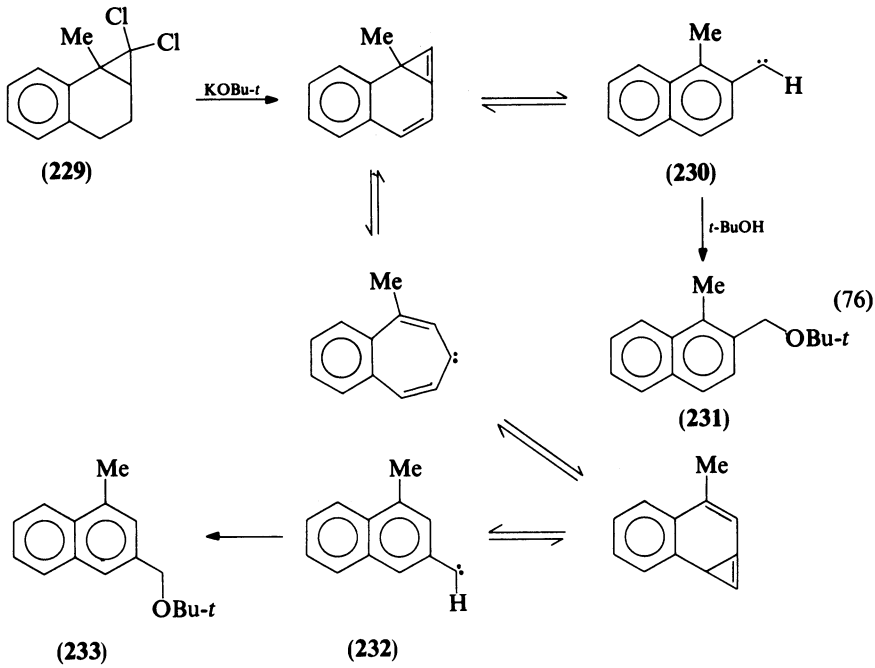


Whilst the existence, energetics and lifetimes of bicyclic intermediates of the type **223** in the mononuclear aromatic series are not formally established[290], it is certain that annelated analogues are true intermediates in various carbene–carbene rearrangements[51, 288–290, 318–320]. Thus, cycloheptatrienylidene **226** gives products expected of the arylcarbene **227** when generated in the presence of carbene traps. However, when formed



in the presence of dienes such as furan typical [2 + 4] adducts of the cyclopropene result[51]. Furthermore, carbene **228** also provides[318] the same product, and cyclopropene[140] must be involved.

Additional evidence for the presence of cyclopropene intermediates in the interconversion of aryl and aromatic carbenes comes from the products of dehydrohalogenation of gem-dichlorocyclopropanes[81]. For example, treatment of cyclopropane **229** with base gives a ca. 1 : 2 mixture of the ethers **231** and **233**, products which are easily rationalized by the pathways shown in equation 76. Of particular significance here is the observation that products derived from both **230** and **232** are obtained. This represents the first definite evidence that bicycloheptatrienes open to both cycloheptatrienylidenes and arylcarbenes under mild conditions, i.e. at ambient temperatures.



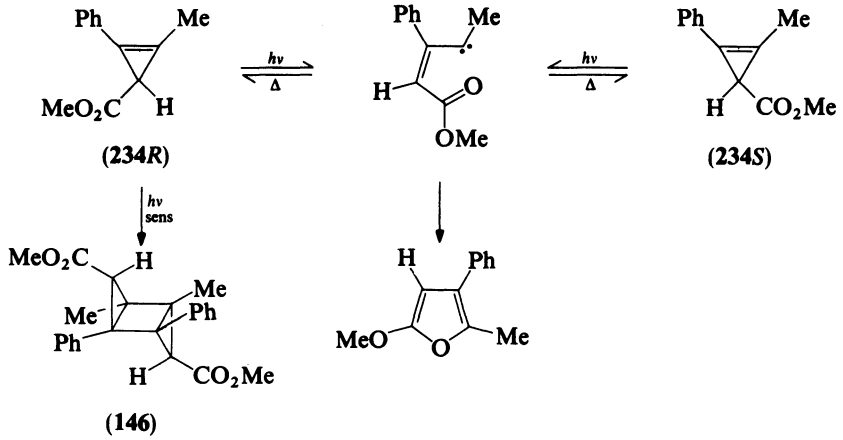
Similar arguments to those outlined above have been put forward to account for the interconversion of arylcarbenes and arylnitrenes[288-290, 319].

2. *Photochemical reactions*

Extensive research[321] has demonstrated that cyclopropenes can undergo four general reaction types on photolysis in solution, namely (a) ring cleavage, (b) side chain cleavage, (c) [2 + 2]cycloaddition (Section IV.A.6b) and (d) intramolecular H transfer. The last two processes are unimolecular triplet state reactions while the first two proceed from the singlet excited state. Thus, the photochemistry of the cyclopropenes is remarkably dependent upon the excited state populated. The present discussion is confined to excited singlet state chemistry with particular emphasis on ring cleavage reactions.

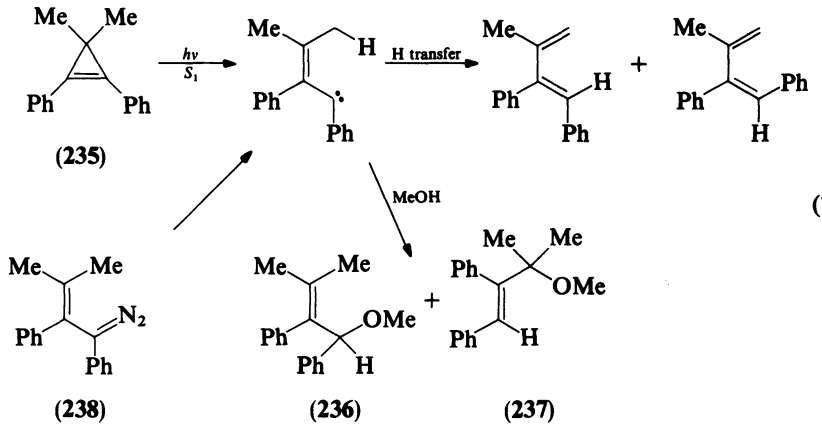
Theoretical calculations[292-294, 322] show that the cyclopropene excited singlet cleaves to vinyl carbene (**193**) ('A') directly whereas the thermal cleavage gives singlet diradical (**191**) ('A") in the first instance. Direct photolysis of cyclopropene must provide singlet **193**[323], since the independently generated triplet form does not undergo ring cleavage[240, 267, 324, 325]. Once formed, **193** can react by various pathways including recyclization[321, 326], intramolecular hydrogen abstraction[327, 328], C–H[329, 330] or O–H[321, 330] insertion, electrocyclization[295, 326, 330-339] and intramolecular cycloaddition[339].

Singlet excited state reactions of cyclopropenes[326, 327] proceed with low quantum efficiencies due to thermal return of carbene **193** to starting material[21, 326] as elegantly illustrated[326] with optically active esters **234**. On photolysis racemization of **234** occurs four times faster than ring cleavage. The photorearranged furan product results from six-electron cyclization of the intermediate carbene and such species have been invoked to account for the interconversion of variously substituted furans[330, 340, 341]. By comparison



(234*R*) (234*S*) (146)

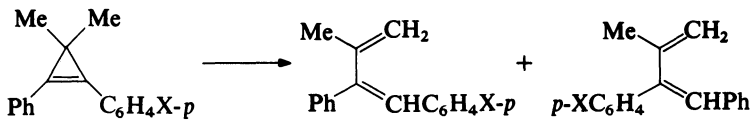
triplet sensitization of **234** provides the [2+2] dimer **146**. Direct photolysis[327] of **235** yields butadienes by H transfer (equation 77). In addition, the formation of the allyl ethers



(235) (238) (236) (237) (77)

236 and **237** from reaction in methanol demonstrates the intervention of carbene as does the formation of the same products from diazo compound **238**.

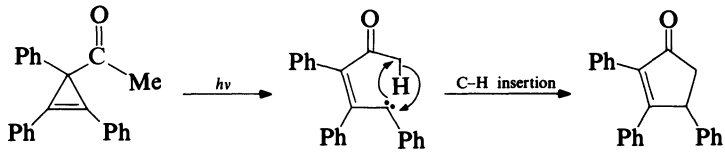
Further support[328] for the intervention of vinylcarbenes in such reactions stems from the cyclopropenes **239** which provide diene products, the proportions of which reflect the facility of the aryl ring to stabilize the developing carbenic centre. The formation[330] of



(239)

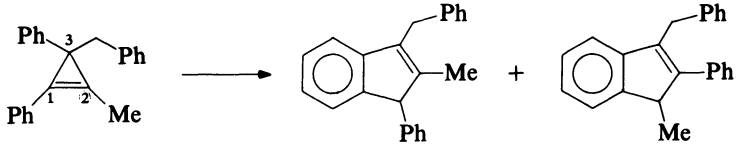
a: X = H	100%	0%
b: X = OMe	74%	26%
c: X = CN	<1%	> 99%

cyclopetanone **241** as the major product from photolysis of acylcyclopropene **240** is similar. Analogous insertion of vinylcarbene into hydroxyl bonds gives dihydrofurans[330] and -pyrans[321].



(240) **(241)**

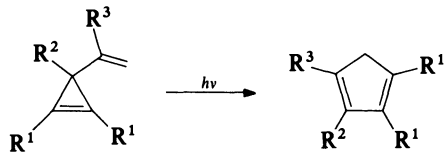
The direct photolysis of 3-arylcyclopropenes gives rise to isomeric indenes[334] and whilst formally analogous to the vinylcyclopropane–cyclopentene rearrangement the reaction can also be effected thermally (Section IV.B.1), by acid (Section IV.B.3) and by transition metal catalysis (Section IV.B.5). One of the first recorded examples[334] involved the conversion **196a–199a** (cf. equation 68). Whilst the vinylcarbene mechanism is analogous to that of equation 68, differences between the thermal and photochemical processes have been noted. Thus[332, 335] thermolysis of the unsymmetrical cyclopropene **242** gives indene **243** exclusively whereas irradiation leads to the alternative indene **244** from regioselective C(2)–C(3) bond cleavage.



(242) **(243)** **(244)**

hv	20%	80%
Δ	100%	0%

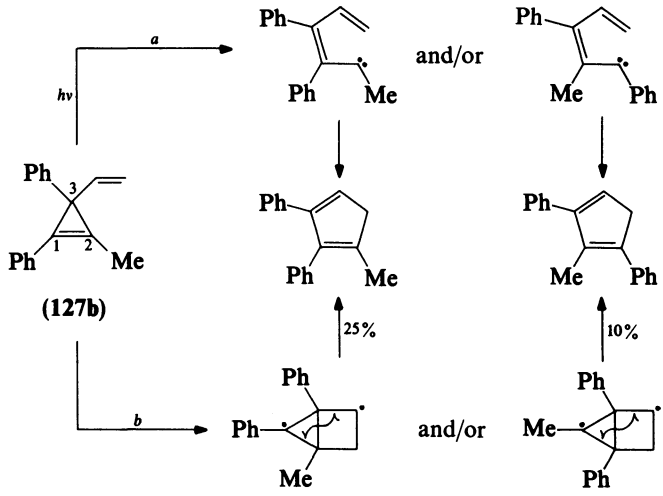
3-Vinylcyclopropenes, e.g. **245a–c**, undergo rearrangements analogous to those of their 3-aryl counterparts[332, 336]. Direct photolyses of the cyclopropenes **127** afford preparatively



(245)

a: R^1 = Ph; R^2 = Me; R^3 = H
b: R^1 = R^2 = Ph; R^3 = H
c: R^1 = Ph; R^2 = R^3 = H

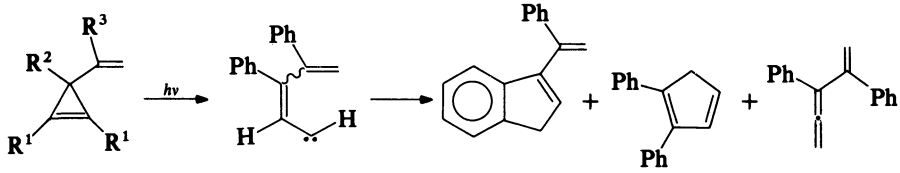
useful yields of cyclopentadienes. Noteworthy is the fact that **127b** rearranges by vinyl rather than phenyl participation. Regioselectivity in ring bond cleavages of unsymmetrically substituted 3-vinylcyclopropenes have been observed[332, 336] and two pathways have been proposed to account for the observation (equation 78). Path *a* requires C(1)–C(3)



(78)

and/or C(2)–C(3) bond cleavage to give carbenes which then cyclize to cyclopentadienes as expected. In path *b* the housane diradicals from π–π bridging in the excited state undergo Grob fragmentation to give the corresponding cyclopentadienes. For 3-arylcyclopropenes analogous routes lead to isoindenes which can aromatize by [1,5]H shift. The effects of the cyclopropene substituents[321] argue for the housane diradical path (path *b*) whereas the products (methoxylated alkenes) obtained by conducting the reactions in methanol are suggestive of carbene intermediates[321] (path *a*). In many respects the two mechanisms (equation 78) differ only in the chronology of bond formation and bond scission. The carbene mechanism begins with bond cleavage and concludes with bond formation, whilst the housane mechanism has these steps reversed. Current thinking[337, 338, 342] suggests that gradations between these two extremes are not only possible but also probable.

Examples of the vinylcyclopropene photorearrangement are known[342] where the chromophore is external to the three-membered ring. The results suggest that the carbene mechanism operates and that it is not contingent upon the chromophore being a part of the carbocycle. For example, direct photolysis of **245d** leads to three photoproducts (equation 79) and the presence of an allene requires a [1, 2]H shift in the carbene intermediate.

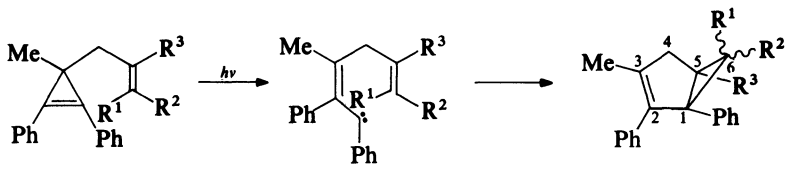


(245)

d: $R^1 = H$; $R^2 = R^3 = Ph$

(79)

The photolysis of 3-allyl substituted cyclopropenes[339, 343] contrasts with their thermal behaviour (Section IV.A.6b). Direct irradiation of **246** affords the bicyclohexenes **248**. Concerted intramolecular cheletropic addition of **247** cannot be involved since both C(6)

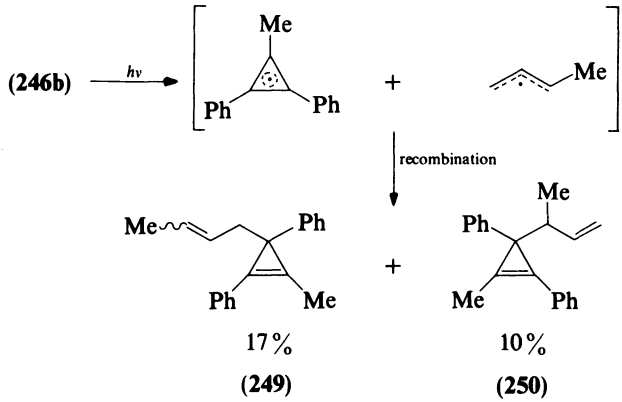


(246) (247) (248)

a: $R^1 = R^2 = H$; $R^3 = Ph$
b: $R^1 = R^3 = H$; $R^2 = Me$
c: $R^1 = Me$; $R^2 = R^3 = H$

epimers of product **248** are formed, and decay of singlet to triplet carbene prior to cyclization is likely.

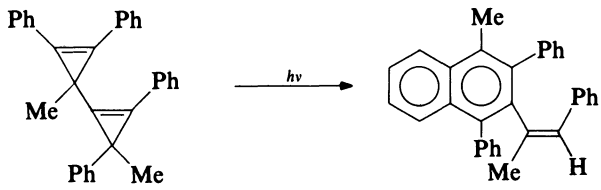
An additional and noteworthy feature of the 3-allylcyclopropene photochemistry is side chain cleavage–recombination with retention of the three-membered ring[329, 339]. The photolysis of **246b** delivers, in addition to the bicyclo[3.1.0]hexene **248b**, the rearranged cyclopropenes **249** and **250**. Homolytic cleavage of the cyclopropenyl-allyl bond and subsequent radical recombination at a phenyl-substituted centre accounts for these observations (equation 80).



(246b) → (249) 17% + (250) 10% (80)

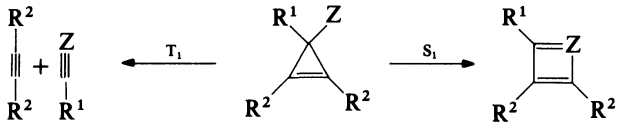
The singlet state photorearrangement of 3-allyl-3-arylcyclopropenes[339] gives indenes exclusively; no bicyclohexenes are observed.

The photochemistry[315] of 1,3′-bicyclopropenyls is in marked contrast to their thermal chemistry (Section IV.B.1); **251** gives naphthalene **252** in 70% yield by a complex pathway.



(251) (252)

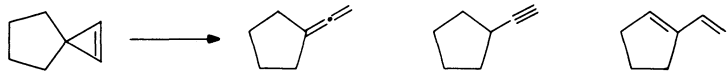
Singlet generated cyclopropyl carbenes, e.g. **253** (Z = C̈R), give cyclobutadienes by Wolff-like rearrangement whereas alkyne products most likely result from the triplet carbene[238, 316, 344–347]. The nitrene analogue **253** (Z = N:) is thought to behave similarly but azacyclobutadiene is not isolable from the S_1 reaction as it fragments to alkyne and nitrile.



(253)

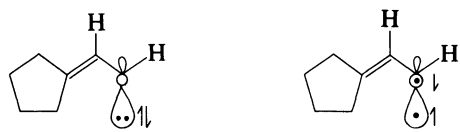
Z = C̈R or N̈:

The majority of investigations of cyclopropene photoreactivity have utilized substrates carrying phenyl, vinyl, or acyl moieties at C(3). In the absence of such substituents the dominant cyclopropene photoreaction involves ring cleavage and although similar to the thermal processes (Section IV.B.1) differences have been noted. Thus, $\pi \rightarrow \pi^*$ excitation (185 nm) of the spirocyclopropene **254** affords a mixture of allene **255**, alkyne **256**, and diene **257**, whereas vapour phase thermolysis at 225°C gives **256** and **257** only[348]. Allene **255** is thermally stable and is therefore not a source of **256** or **257**. The difference in



(254)		**(255)**	**(256)**	**(257)**
	hv	34%	26%	8.1%
	Δ	0	75%	3.5%

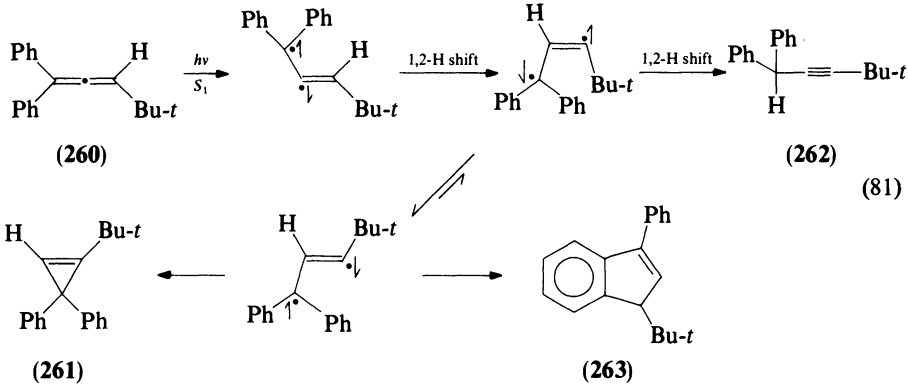
product distributions is attributed to selective reactivity of the ground and first excited state singlet vinyl carbenes, **258** and **259** respectively, formed upon ring cleavage of the cyclopropene. The least favourable thermal motion leads to allene **255** and this most



(258) **(259)**

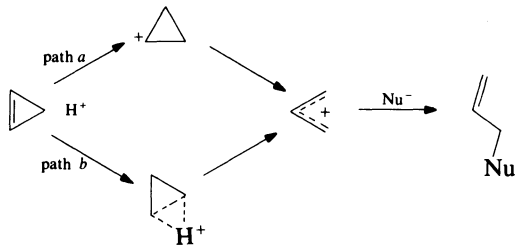
closely approximates to the S_1 excited state potential surface. Thus allene formation is photochemically preferred. Nonetheless, a considerable proportion of the photoreaction must proceed by collapse of **259** to **258** since the ratio of **256** : **257** is of the same order from both reactions.

The importance of cyclopropene as an intermediate in the thermal isomerization of allene to propyne is matched in the photorearrangements of 1,1-diarylallenes, e.g. **260**, which give cyclopropenes, e.g. **261**, alkynes, e.g. **262**, and indenes, e.g. **263**, as the primary photoproducts[349]. The proposed mechanism (equation 81) requires two consecutive H shifts to give **262**, whilst bond rotation after one such shift provides a less congested diradical which has cyclization paths available to it to give **261** and **263**.



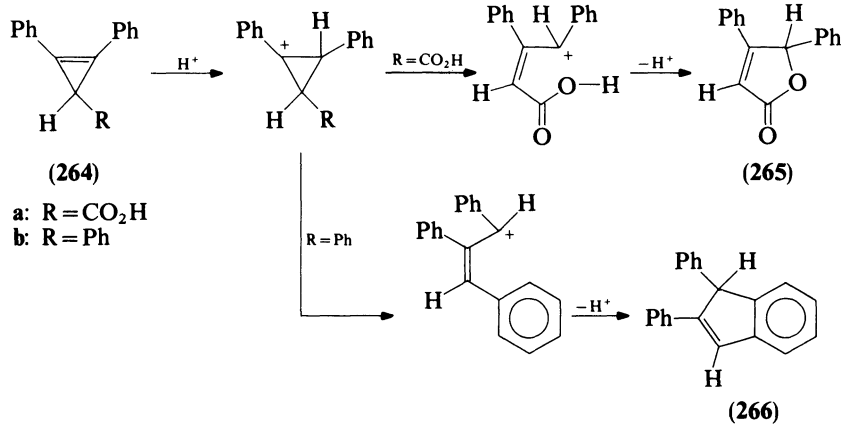
3. *Reactions with electrophiles*

Cyclopropenes are readily cleaved by acids. The reactions are rationalized either by initial protonation of the double bond and subsequent electrocyclic ring-opening of the cyclopropyl cation thus formed (path *a*, equation 82), or by protonation of a cyclopropene σ bond to give the allylic cation more directly (path *b*, equation 82)[9,350]. The final products of reaction are derived from nucleophilic capture of the allyl ion.



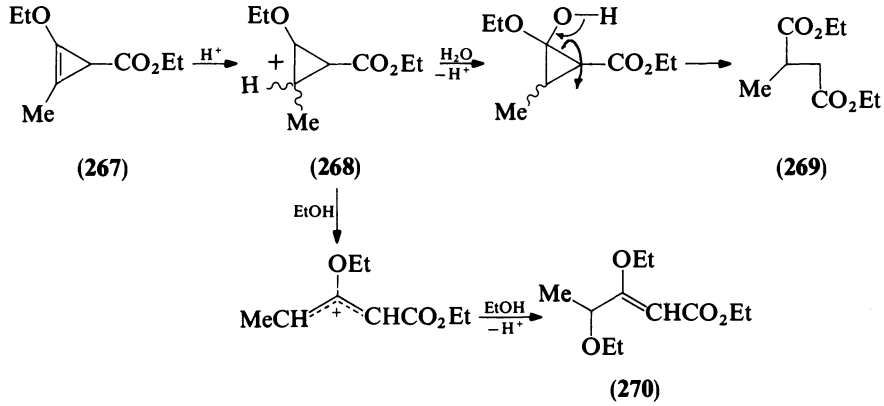
(82)

The polymerization of naturally occurring sterculic acid (**2**) in the presence of proton sources has been known[9] for over 40 years and proceeds[351] via acid-catalysed opening of the cyclopropene ring. The rearrangement of carboxylic acid **264a** to lactone **265** is



rationalized[352] in terms of initial protonation of the cyclopropene double bond and the acid-catalysed conversion[352] of **264b** into indene **266** most likely proceeds in a similar manner.

Whilst treatment of the cyclopropene **267** with aqueous acid gives succinate **269**, reaction[353] with ethanolic acid gives the α,β-unsaturated ester **270**. This divergent reactivity reflects subtle behaviour of the protonated intermediate **268**. Whereas the



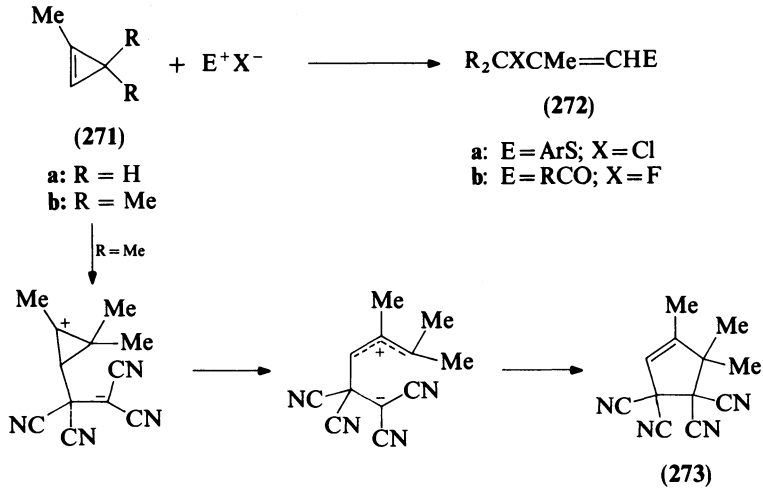
(267) **(268)** **(269)**

(270)

expected ring-opening to allyl cation occurs in ethanol, in water hydration is more rapid and the resultant hemiacetal cleaves in strict analogy[353] to the acid-catalysed scission of other β-oxycyclopropylcarbonyl compounds.

The steroidal cyclopropenes **4–6** provide isomeric butadienes by initial protonation and proton loss from the corresponding allyl cation. A detailed study[21] indicates that regioselective σ-bond fission takes place because of steric hindrance to protonation by the bulky steroid ring from one side.

In addition to protic acids other electrophiles promote cyclopropene ring cleavage via the derived cation. Thus, 1-methylcyclopropene **271a** reacts with 2,4-dinitrophenylsulphenyl chloride to give alkene **272a** amongst other products[224] and cyclopropene **271b**



(271)

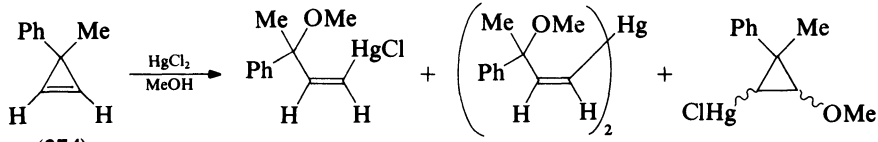
a: R = H
b: R = Me

(272)

a: E = ArS; X = Cl
b: E = RCO; X = F

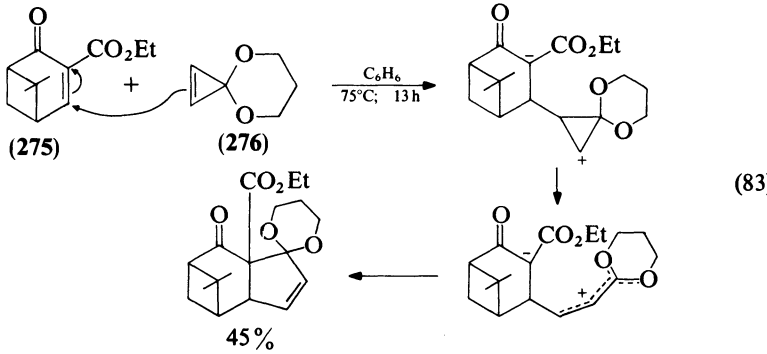
(273)

reacts with various acyl tetrafluoroborates to give α,β-unsaturated carbonyl compounds, e.g. **272b**[354]. With tetracyanoethylene **271b** gives[355] cyclopentene **273** as shown. Methoxymercuration gives rise to ring-cleaved products[356] as illustrated for **274**.



(274)

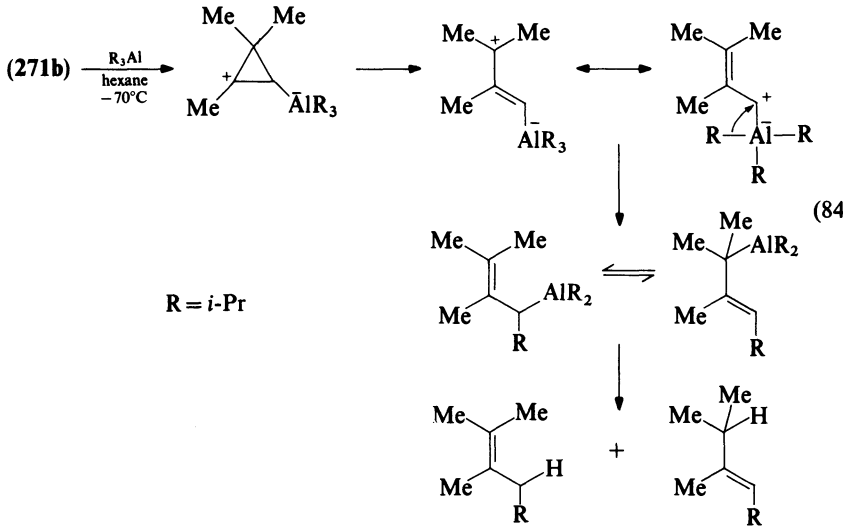
Annelation of a three-carbon unit derived from cyclopropenone acetals across the sp^2 carbon atoms of electron-deficient olefins has provided a simple new cyclopentenone synthesis[357]. Thus, a 1 : 1 mixture of the α,β-unsaturated ketone **275** and acetal **276** affords



(275) **(276)** **(277)** 45%

(83)

the cyclopentenone acetal **277** (equation 83). Electrophilic attack of **275** on **276** to give zwitterionic intermediates and subsequent bond reorganization accounts for the process.



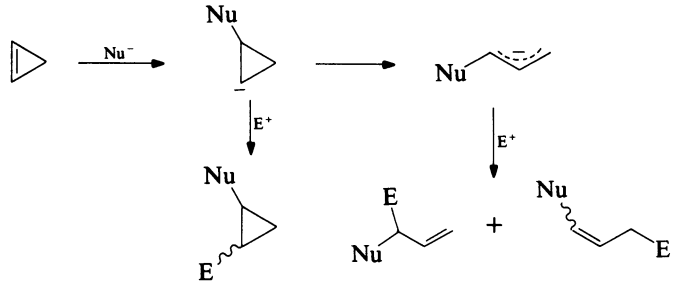
R = *i*-Pr

(84)

Carbalumination of **271b** with tri-isopropylaluminium affords[358] acyclic products, the formation of which can be attributed to rearrangement of the initially formed cyclopropyl carbocation (equation 84). Ring-opened products also result from reactions with trialkylboranes, but only cyclopropanes, from addition to the π bond, are seen in reactions with organomagnesium reagents[358].

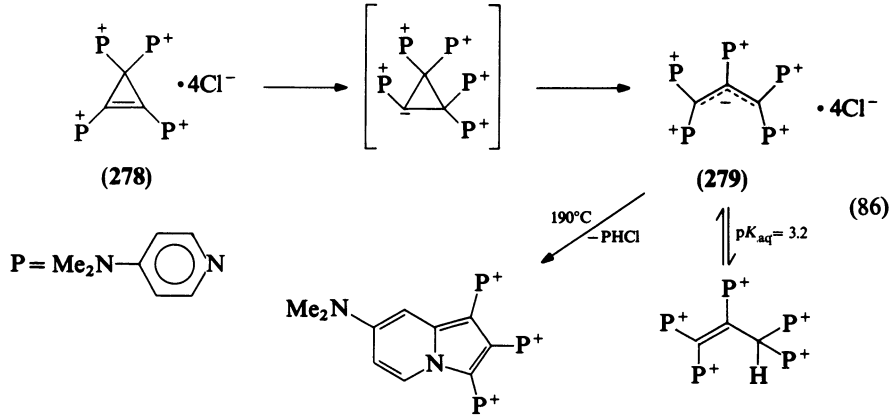
4. Reactions with nucleophiles

As noted earlier (Section IV.A.5), the addition of nucleophiles to cyclopropenes relieves ring strain. Electrocyclic opening of the anion generated in this manner competes with capture by an ambient electrophile (E^+) (equation 85). Cyclopropene **278** reacts[359] with



(85)

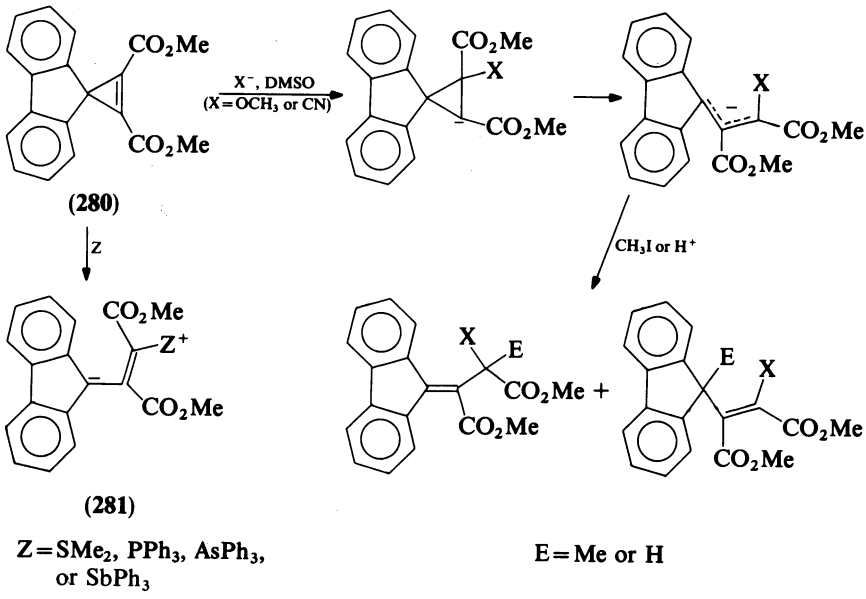
4-(dimethylamino)pyridine to give the air-stable allyl anion **279** as dark red crystals. The reaction presumably proceeds as illustrated (equation 86). Anion **279** can be diverted to alkene by proton (HCl or HBF_4) or rearranged to indolizine.



(86)

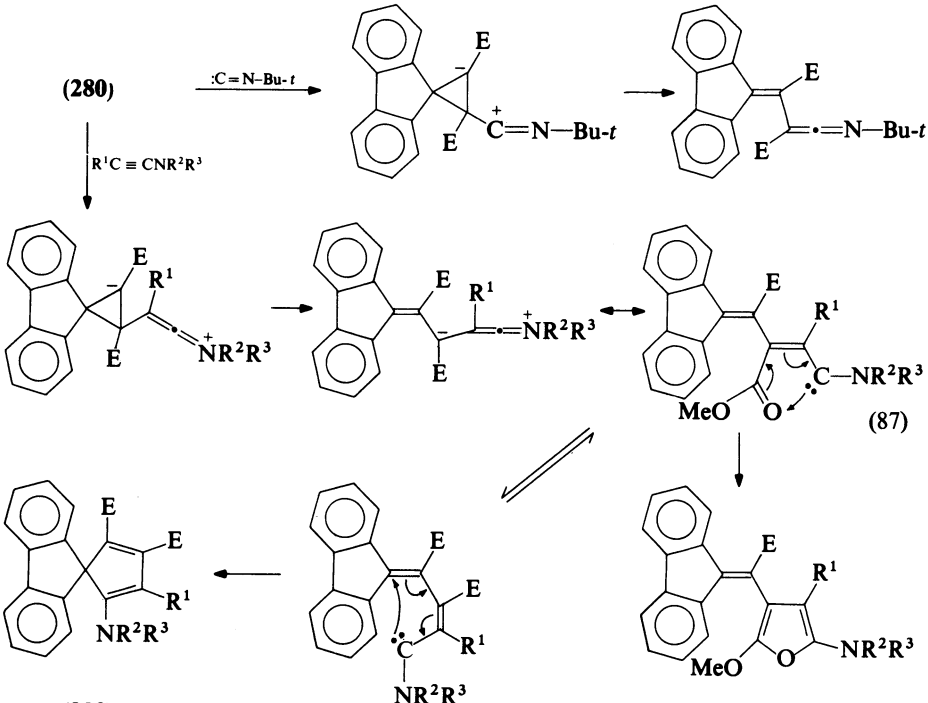
The addition of methoxide or cyanide ions to cyclopropene **280** gives[360] mixtures of isomeric alkenes upon methylation or protonation via allyl anions. However, triphenylphosphine, -arsine, or -stibine, and dimethyl sulphide afford the corresponding ylides **281**. Photochromic 1,8a-dihydroindolizines result[361] from reaction of spiroannelated cyclopropenes of the type **280** with pyridines. The synthesis proceeds to ylides of the type **281** which cyclize to give the observed products.

Nucleophilic addition[362] of *t*-butylisocyanide to cyclopropene **280** gives vinylketenimines but the same cyclopropene with ynamines affords mixtures of furan **282** and



(281)

Z = SMe_2, PPh_3, $AsPh_3$, or $SbPh_3$



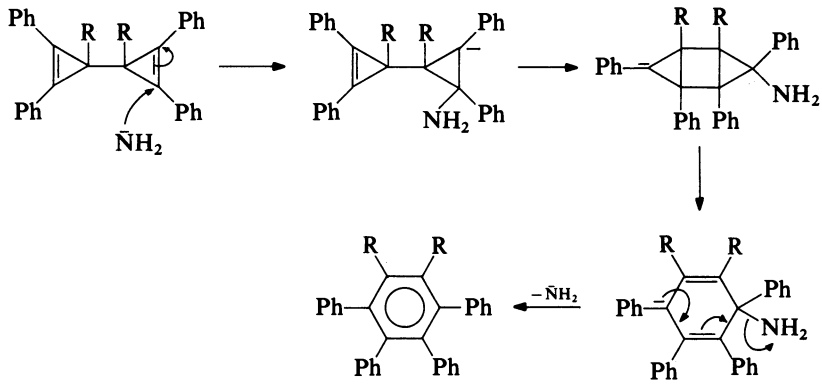
(283)

(282)

E = CO_2Me

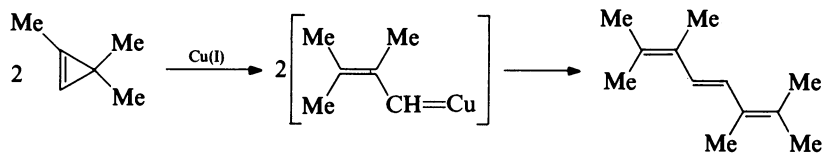
cyclopentadiene (**283**). Initial nucleophilic attack and electrocyclic ring-opening gives zwitterionic/carbenic intermediates which cyclize to the observed products (equation 87).

The aromatization[363] of 3,3'-bicyclopropenyls can be effected by amide ion as illustrated below:



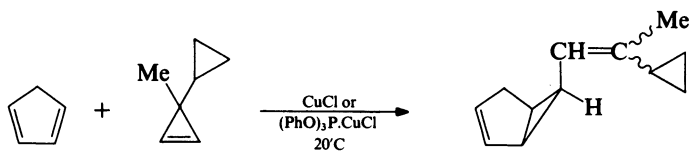
5. *By metal catalysis*

Metal-catalysed rearrangements of cyclopropenes are well known[364,365] and the resultant products suggest that vinylcarbenoid intermediates are involved. The Cu(I) catalysed conversion of 1,3,3-trimethylcyclopropene (**271b**) into triene **284** involves[366] dimerization of complexed carbene. Related processes are promoted[366,367] by Hg(II) and



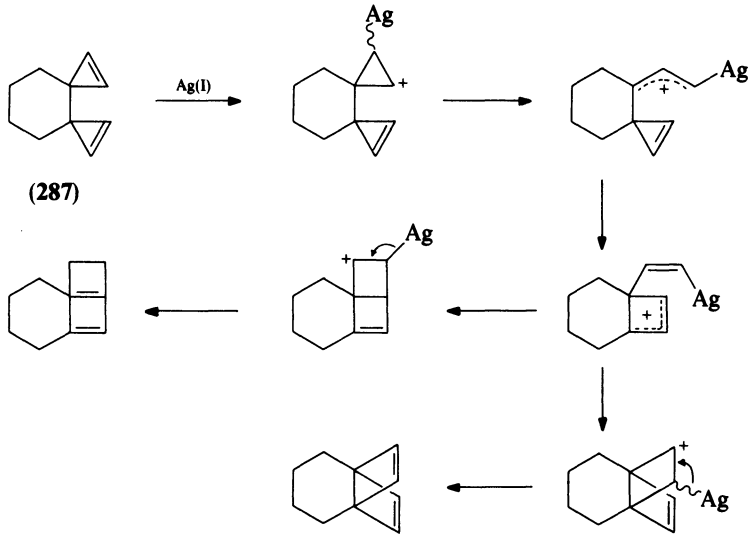
(**271b**) (**284**)

Tl(III) and the intervention of carbenoid species is supported by the isolation of cyclopropanes in the presence of added olefins. Thus, **285** gives[368] bicyclohexene **286** in the presence of cyclopentadiene (equation 88); similar results obtain from other Cu(I) salts[369] or Ni(O) complexes[370].



(**285**) (**286**) (88)

The Ag(I)-catalysed rearrangement of 3,3'-bicyclopropenyls to the Dewar benzene system is well established[371–373]. For example, reaction of the annelated system **287** affords ring-fused Dewar benzenes with catalytic amounts of Ag(I).

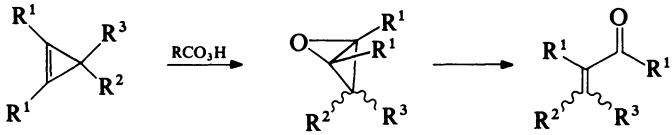


(287)

Conversions of 3-arylcyclopropenes into indenes using Ag(I) and Pd(O) have been reported[374, 375]. The silver-catalysed opening of the three-membered ring in cyclopropabenzene proceeds[376] via a benzylic carbocation.

6. By oxidation

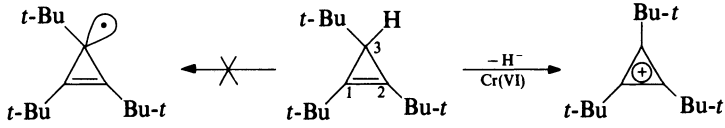
Although definitive evidence for the intermediacy of oxabicyclobutanes in the peracid oxidation of cyclopropenes is lacking, the production of conjugated carbonyl compounds from such reactions is most readily rationalized from the formation and spontaneous rearrangement of such species (equation 89)[377–385]. Calculations[378] suggest that oxabicyclobutane should display a preference for disrotatory over conrotatory ring-opening, and early product studies[380] were taken to imply that the disrotatory mode leading to a transoid enone conformer is preferred over that which gives the cisoid counterpart. However, more recent work[385] suggests a stepwise conversion of the oxabicyclobutane moiety into the enone products; possible intermediates are oxatenes or diradicals. When the cyclopropene carries non-equivalent substituents at C(3) (equation 89; $R^2 \neq R^3$) peroxidation produces geometrical isomers of the enone product in ratios which probably reflect subtle substituent interactions[379].



(89)

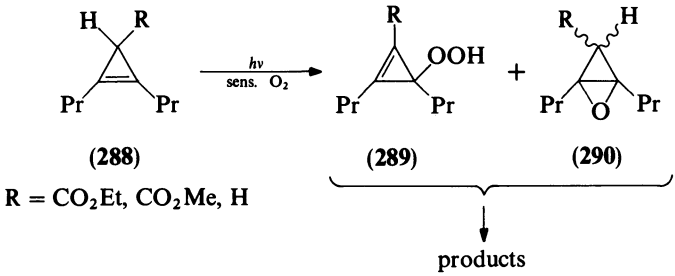
R^1 = Me, Et, Ph
R^2, R^3 = Me, Et, CO_2Me, CO_2Et, CH_2OH, CH_2OMe

The remarkable preference of 1,2,3-tri-*t*-butylcyclopropene to produce cyclopropenium ion by C(3)–H bond cleavage rather than suffer oxidation at the double bond with Cr(VI) is attributed to direct hydride ion transfer to Cr(VI). The process is promoted by aromatic



stabilization of the transition state structure[386]. The usual process by which Cr(VI) oxidizes C–H bonds involves hydrogen atom abstraction but with this substrate the corresponding σ radical derives no particular (aromatic) stabilisation (Section VIII.B).

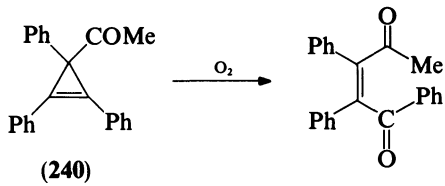
Whilst 1-methylcyclopropene is inert[387] towards singlet oxygen, the photosensitized oxidation[388] of cyclopropenes **288** rapidly produces numerous products which include enones. This latter free radical oxidation is thought to provide **289** and **290** which afford products by secondary rearrangement; singlet oxygen is not involved in these reactions.



(288) **(289)** **(290)**

R = CO_2Et, CO_2Me, H

Facile atmospheric oxidation[330] of 3-acylcyclopropenes, e.g. **240**, results in the corresponding α,β-unsaturated carbonyl compound. Pathways involving oxabicyclobutanes, oxetanes or cyclopropyl radicals account for the observed product but no distinction between them is presently possible.



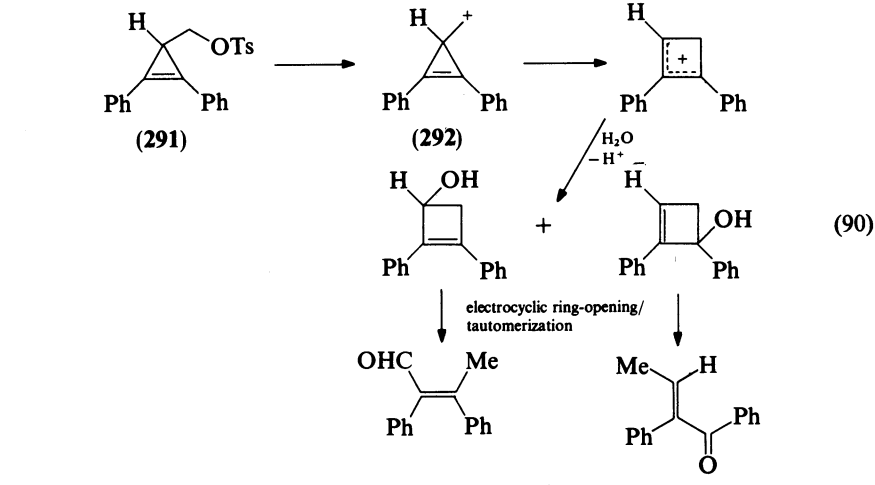
(240)

7. Cyclopropenylcarbinyl cation intervention

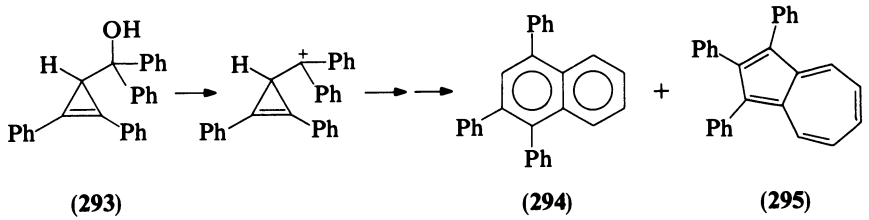
Although the reactions of cyclopropylcarbinyl cations have been investigated in considerable detail, corresponding reactions of the cyclopropenyl system have received much less attention, but they appear to be similar[389]. Solvolysis of tosylate **291** proceeds only three times more rapidly than its saturated analogue; α,β-unsaturated carbonyl compounds ensue, presumably from ring expansion of cation **292** (equation 90). Analogous processes account for the first steps of the dehydration of **293** to naphthalene **294** and azulene **295**[390, 391] under various conditions as shown opposite.

V. ORGANOMETALLIC DERIVATIVES

The reactions of cyclopropenes with metal complexes proceed either with ring retention or with cleavage of the C(1)–C(3) σ bond.



(90)



(293) (294) (295)

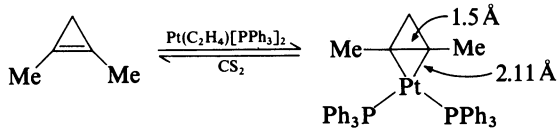
A. Complexation with Ring Retention

Because of the reduction in double bond character, and hence ring strain, complexation of cyclopropenes to metal centres takes place readily. Although no simple relationship between strain and complexing ability has been developed, the argentation constant for cyclopropene[392] ($K_{Ag} > 10^7$) as determined from the expression

$$K_{Ag} = [\text{Ag(olefin)}^+]\text{aq}/[\text{Ag}^+]\text{aq}[\text{olefin}]_{CCl_4}$$

is $\sim 4 \times 10^7$ higher than that of norbornene ($K_{Ag} = 0.265$) and $\sim 5 \times 10^8$ higher than (strainless) cyclohexene ($K_{Ag} = 0.0184$).

The first cyclopropene transition metal complexes isolated were stable Pt(0) species, e.g. **296**. These are obtained from the displacement of ethylene in various platinum complexes by cyclopropene[393] and analogous Ni(0) complexes are now available[394]. The dominant bonding is of the π-type with the lengthened C(1)–C(2) bond reflecting a significant relief of strain upon complexation. Complex **296** liberates the cyclopropene upon treatment with carbon disulphide.

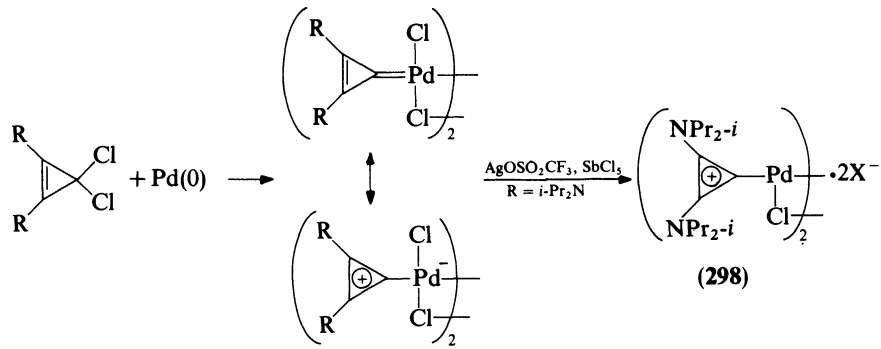


(296)

Reaction of $NbCl_2(\eta^5\text{-}C_5H_5)_2$ with sodium metal in the presence of cyclopropene delivers $NbCl(C_3H_4)(\eta^5\text{-}C_5H_5)_2$ which is reduced on subsequent treatment with hydrochloric acid and almost pure cyclopropane[395] is obtained.

Although η^3-cyclopropenylnickel complexes are generally formed upon reaction of 3-halocyclopropenes with Ni(0) species[396] asymmetric (η^2) π co-ordination is known[397].

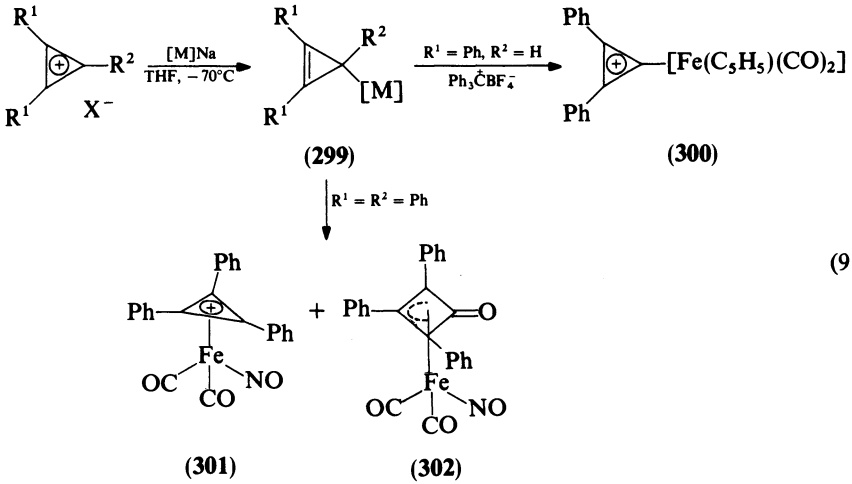
The reaction of palladium black with certain gem-dichlorocyclopropenes produces the cyclopropenylidene–palladium(II) chloro-bridged complexes **297** which have a significant contribution from the zwitterionic form[398–401]. The unsaturated complex **298** can be



(297) **(298)**

R = NMe_2, Ph, *t*-Bu, *i*-Pr, N(Pr-*i*)$_2$, X^- = $SbCl_6^-$, $CF_3SO_3^-$

obtained by chloride ion abstraction from **297** (R = *i*-Pr_2N) with a strong Lewis acid[399]. Similar reactions with Pt(0)[402], $Na_2Cr(CO)_5$[403] and $Na_2Mo(CO)_5$[403], lead to analogous cyclopropenylidene complexes. The Fe(II) derivatives **299a** are available from cyclopro-



(299) **(300)**

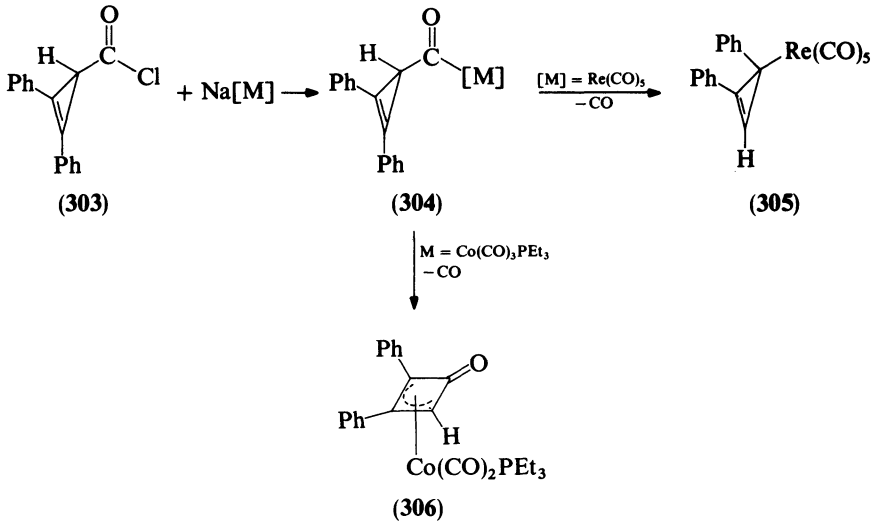
(301) **(302)** (91)

a: M = $[Fe(C_5H_5)(CO)_2]$; R^1 = *t*-Bu, Et_2N, *i*-Pr_2N; R^2 = H, Me, OMe, Cl; X = BF_4, Br, ClO_4, FSO_3

b: M = $[Fe(CO)_3NO]$; R^1 = R^2 = Ph; X = Br

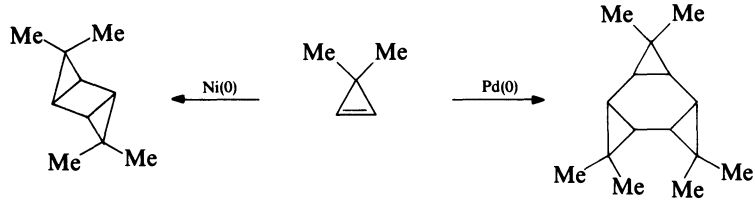
penium salts (equation 91) and complex **299a** (R^1 = Ph; R^2 = H) gives the (σ-2,3-diphenylcyclopropenylidene)iron salt **300** upon hydride ion abstraction[404]. Analogue **299b** is labile, however, and gives complex **302** by ring expansion, and the η^3-derivative **301** by decarbonylation[405,406].

Whilst reaction of acyl chloride **303** with Na[$Co(CO)_3(PEt_3)$] affords the oxocyclobutenyl complex **306**[407] by ring expansion and CO loss, analogous treatment with $NaRe(CO)_5$ delivers the non-fluxional η^1-cyclopropenylrhenium compound **305**[408]. In the latter case, compound **304** loses carbon monoxide with concomitant migration of the cyclopropenyl moiety from carbonyl to rhenium as an allylic rearrangement rather than a 1,2-shift.



(303) (304) (305) (306)

Extensive work by Binger[365,409] has shown that palladium, nickel and rhodium complexes can effect the cyclooligomerization of alkylated cyclopropenes. The mode of coupling is often dependent upon the particular metal catalyst employed (equation 92).

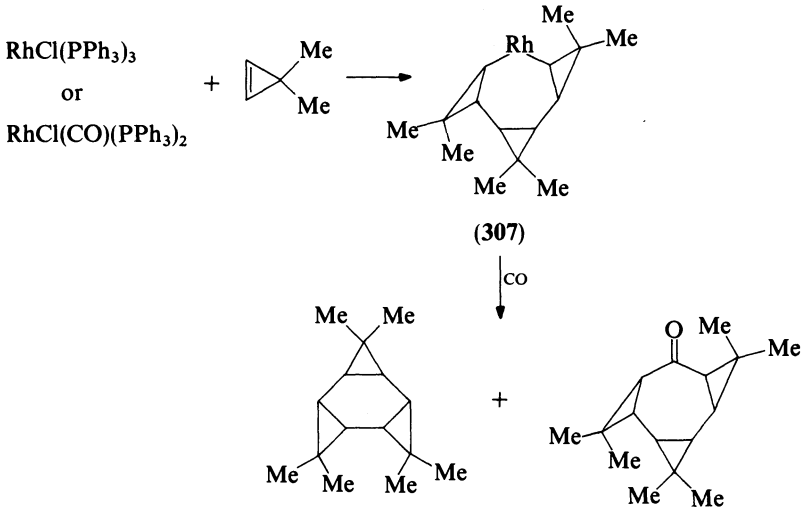


(92)

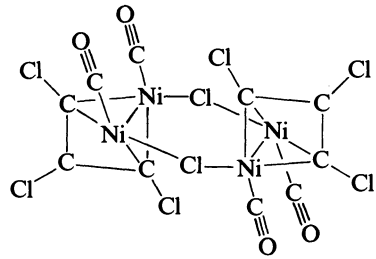
Metallacycles, e.g. **307** (see next page), are intermediates in these processes and several have been isolated and characterized crystallographically. In addition, certain of these species may be carbonylated to give cyclic ketones.

B. Complexation with Ring Cleavage

As noted above (Section IV.B.5) various metal complexes including Ni(0)(cyclooctadiene)$_2$ catalyse cyclopropene ring cleavage reactions and deliver products by way of

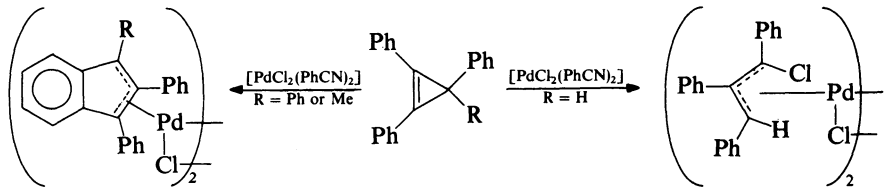


complexed vinylcarbenes. In contrast, reaction of tetrachlorocyclopropene with stoichiometric amounts of $Ni(0)(CO)_4$ affords the shock sensitive complex **308** which has a planar Ni_4Cl_2 ring with two ring-opened C_3Cl_3 fragments bridging the two pairs of nickel atoms[410].



(308)

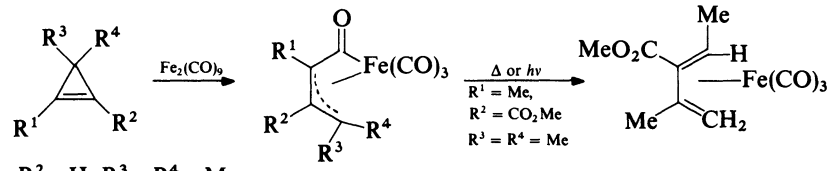
Cyclopropenes react with palladium(II) compounds to give π allyl complexes; 1,2,3-triphenylcyclopropene forms the ring-opened product **310** (equation 93), whilst its 3-methyl and tetraphenyl counterparts give[375,411] indenyl complexes **309**.



(309) **(310)**

(93)

Di-irononacarbonyl reacts with numerous cyclopropenes to give (η^3:η^1)iron complexes **311**. The products, characterized by crystallographic methods, result from ring-opening and carbonylation[412] with a regiochemical outcome dominated by steric factors. However, electronic factors are also very important and complexes **311** with electron withdrawing substituents are thermally and photochemically labile; decarbonylation and rearrangement occurs to give diene complexes **312**[413].



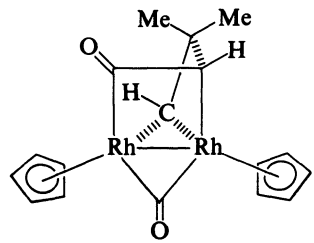
$R^1 = R^2 = H$; $R^3 = R^4 = Me$
$R^1 = R^3 = R^4 = Me$; $R^2 = H$
$R^1 = R^2 = R^3 = Ph$; $R^4 = H$

(311)

(312)

$R^1 = t$-Bu; $R^2 = MeCO$; $R^3 = R^4 = Me$
$R^1 = MeCO$; $R^2 = CH{=}C(Me)_2$; $R^3 = R^4 = Me$
$R^1 = CO_2Me$; $R^2 = H$; $R^3 = R^4 = Me$

Reaction of tetrachlorocyclopropene or 3-methoxytrichlorocyclopropene with $Rh(CO)Cl(PMe_2Ph)_2$[414] and reaction of 3,3-dimethylcyclopropene with $Mo_2(C_5H_5)_2(CO)_4$[415] or $[Mo(\eta\text{-MeC}{\equiv}CMe)(PhS(O)SPh)(\eta\text{-}C_5H_5)]$[416], produce complexes derived from fission of the cyclopropene C(1)–C(3) bond. However, treatment of the last of these carbocycles with the binuclear rhodium complex $[Rh_2(\mu\text{-}CO)_2(\eta\text{-}C_5Me_5)_2]$ results in the cleavage of the carbon–carbon double bond and formation of the bridged carbene complex **313**[417].



(313)

C. Theoretical Aspects

Few theoretical studies have been performed on organometallic derivatives of cyclopropenes. However, INDO SCF MO calculations on π-cyclopentadienyl-π-cyclopropenylnickel indicate[418] the metal atom to have formal d^{10} configuration, while an MNDO study on beryllium derivatives of $(CH)_n$ carbocycles predicts no minima corresponding to η^3 derivatives when $n = 3$ and suggests that the beryllium atom inserts into the ring[419]. An HMO comparison of sandwich complexes of the dicyclopropenyl, diallyl and allylcyclopropene type show that the first type is most stable[420]. *Ab initio* SCF MO calculations using the STO-3G and 3-21G basis sets have provided the geometries and the strengths of the cap (= X) ring interactions in the half sandwich molecules **314**[421].

(314)

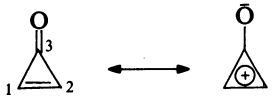
X = Be^-, BH^-, CH, NH^+, N

VI. ASPECTS OF CYCLOPROPENONE CHEMISTRY

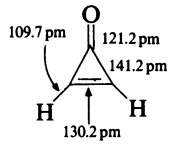
Because of its position as the first member of the $(4n+3)$ annulenone series[422], cyclopropenone (**56**) has been the subject of much interest[114]. The diphenyl derivative **14** was the first of the cyclopropenones to be isolated[423] and because of its stability and ready availability it remains the most studied cyclopropenone[114]. Compound **14** is a strong contact sensitizer[424] which causes allergies and brings out blisters on the skin, and it is also an *in vitro* stimulator of the activity of microsomal epoxide hydrase[424]. Parent **56**, reported[425] in 1967, is stable for long periods below its melting point (−29 to −28 °C) when pure, but it polymerizes at higher temperatures; organic solutions of **56** have moderate stability at ambient temperatures.

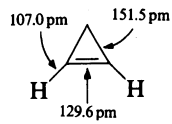
A. Physical and Theoretical Aspects of Cyclopropenones

Considerable effort[114] has been expended to assess the contribution of the dipolar cyclopropenium oxide form (**56b**) to the resonance hybrid of the molecule. However, such



(**56a**) (**56b**)





aspects of cyclopropenone chemistry are particularly pertinent to a discussion of the 2π cyclic aromatic species, a description of which is to be found in Chapter 24. Nonetheless, relevant data are presented at this point, albeit briefly.

Structural studies[426] show that the σ ring bonds of cyclopropenone are shorter than their cyclopropene counterparts, whilst the carbonyl bond is longer than model compounds. These effects are consistent with extensive π delocalization[427] and the high dipole moments (4.7–5.1 D)[427], low pK_b values[427] and low field (~ 9.0 ppm) proton resonances[425] support[427] significant aromatic stabilization.

Various molecular orbital calculations[426,428–430] provide plausible stabilization energies for cyclopropenone. Photoacoustic[431] and bomb[426] calorimetry have provided the heat of formation of diphenylcyclopropenone as 350 ± 16 and 354 ± 21 kJ mol^{-1} respectively, which leads[431] to a stabilization energy of 46 kJ mol^{-1}. In contrast, the physical and spectroscopic properties of the cyclopropenones have been explained[432] without recourse to aromatic stabilization, but this is contrary to what is generally accepted.

The NMR spectra of the cyclopropenones display[425,426,433–435] a low field resonance (ca. 9.0 ppm) for the vinylic hydrogen atom and signals at ca. 155 and 158 ppm for the CO and CH= moieties. In the infrared three intense and characteristic[114,436–439] bands are observed. In the 1830–1870 cm^{-1} range, an out-of-plane stretching vibration of the two unsaturated linkages is observed and this has a predominance of the C=O coordinate. A band in the range 1600–1660 cm^{-1} is due to the corresponding in-phase vibration with a preponderance of the C=C coordinate. A symmetric stretching of the ring σ bonds occurs

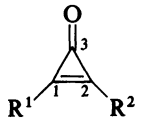
at ca. 880 cm^{-1}. Parent **56** proves to be an exception, and has bands at 1864, 1833 and 1480 cm^{-1}. The 1480 cm^{-1} band is due to the carbon–carbon bond frequency with strong vibrational coupling. Calculations, taken in conjunction with the infrared and Raman data, suggest[438] a 30% contribution to the ground state of **56** by the polar form **56b**.

The electronic spectra of several cyclopropenones have been studied both theoretically[114,440] and experimentally[441-443]. An analysis of the photoelectron (pe) spectra of **56** and its diphenyl and di-*t*-butyl derivatives suggests[441] a significant stabilizing interaction between the unsaturated moieties and a resemblance to cyclopropenium ions. Parent **56** exhibits bands at 8.23 and 9.61 eV. Ionization from the lone pair (n) MO accounts for the former band while the latter arises from ionization of the π (b_1) MO localized mainly on the C=C bond. Consistent with theoretical predictions that the relatively high energy cyclopropene antibonding orbital shifts the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions to low wavelengths[442], the UV absorption spectra of dialkylcyclopropenones show only strong end (< 175 nm) absorption for the $\pi \rightarrow \pi^*$ transition. The parent molecule displays an $n \rightarrow \pi^*$ absorption at 276 nm ($\varepsilon = 31$) and a $\pi \rightarrow \pi^*$ band below 190 nm[443].

B. Reactions of Cyclopropenones

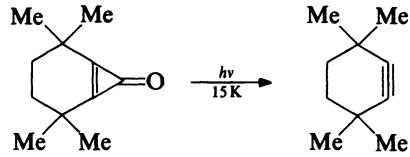
1. Decarbonylation

Loss of carbon monoxide from the cyclopropenones (equation 94) can be effected thermally[116,434,444], photochemically[442,445,447] and by metal catalysis[446], and has often provided a useful route to otherwise inaccessible alkynes. The thermal cheletropic ejection



$$\longrightarrow \quad R^1{-}C{\equiv}C{-}R^2 + CO \qquad (94)$$

of carbon monoxide is expected to be unfavourable from orbital symmetry considerations, and in fact only takes place at temperatures in excess of 130°C. In general, diarylcyclopropenones decarbonylate at lower temperatures than dialkylcyclopropenones. The photochemically promoted process has been used to produce small ring cycloalkynes as illustrated below (equation 95)[442,447]. The photolytic preparation of benzocyclopropenone is foiled, except under matrix conditions, because of facile decomposition to

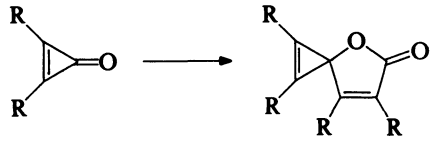


(95)

dehydrobenzene and carbon monoxide[93,448]. A variety of metal carbonyls including $Ni(CO)_4$, $Co_2(CO)_8$, $Fe_2(CO)_9$, and $Fe_3(CO)_{12}$ effect decarbonylation and the reaction most likely proceeds via metallacycles, e.g. **315**[114,446].

(315)

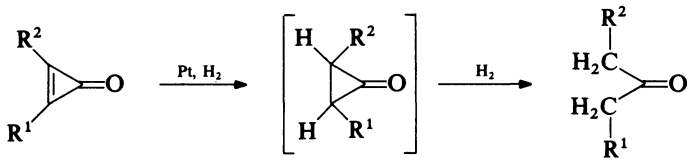
When cyclopropenone, or its dichloro or diphenyl analogues are heated to ca. 100°C dimerization, rather than decarbonylation, takes place and spirocyclic compounds (**316**) are obtained. These most likely result from nucleophilic attack on the carbonyl carbon of one molecule by the oxygen atom of the second followed by 1,2-cleavage and cyclization[444, 449].



R = H, Cl, Ph (316)

2. Reduction

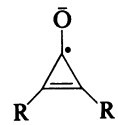
The catalytic hydrogenation of various cyclopropenones gives acyclic ketones **318** via the corresponding cyclopropanone intermediate **317**[434, 442, 444, 445]. In contrast, Pd/C promoted reaction of di-*n*-propylcyclopropenone delivers the α,β-unsaturated aldehyde



(317) (318)

$R^1 = R^2$ = Ph, Pr, *t*-Bu, H; R^1 = H, $R^2 = C_5H_{11}$.

resulting from hydrogenolysis of the C(1)–C(3) bond[442]. Whilst both the carbonyl group and the cyclopropenone double bond of diphenylcyclopropenone are reduced by lithium aluminium hydride[423], selective reduction of the double bond in ethylphenylcyclopropenone occurs with sodium borohydride[450]. Treatment of cyclopropenone with sodium amalgam[449] and diphenylcyclopropenone with aluminium amalgam or magnesium–magnesium iodide[451] generates the corresponding radical anion (**319**) which undergoes pinacolic coupling to give the 3,3′-bicyclopropenyl. Subsequent aromatization of these latter species (Section IV.B.1) yields hydroquinone and tetraphenylresorcinol



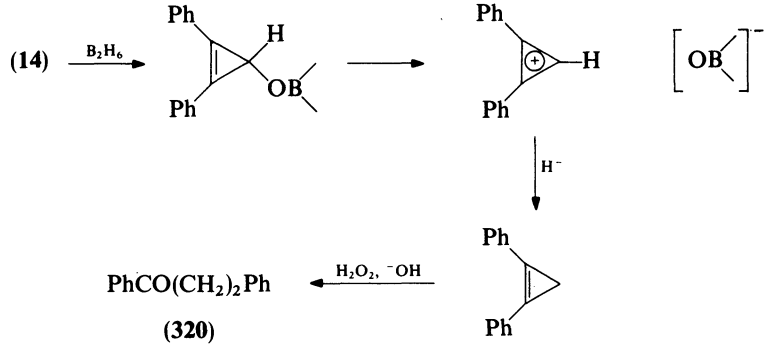
(319)

a: R = H
b: R = Ph

respectively. Radical anion **319b**, characterized by ESR spectroscopy[452], has also been generated from reduction of the cyclopropenone with lithium in hexamethylphosphoric

triamide, by electrolytic reduction in dimethylformamide, and by electron transfer from the base system dimethyl sulphoxide/potassium *t*-butoxide; its ultimate fate depends upon the mode of generation[452].

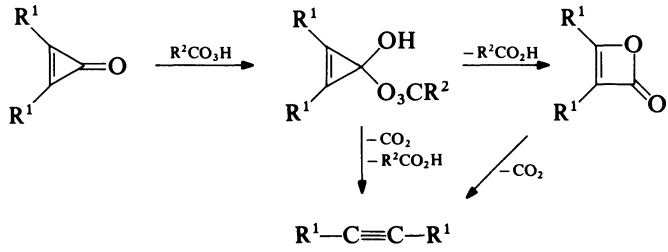
Diborane reduction of diphenylcyclopropenone followed by alkaline peroxide treatment provides[453] *β*-phenylpropiophenone (**320**) and diphenylcyclopropene is a likely intermediate (equation 96).



(96)

3. Oxidation

Various cyclopropenone derivatives react with peracids to yield the corresponding alkynes as primary products. However, the alkynes are themselves oxidized under the reaction conditions and the reaction is impractical as an alkyne synthesis. Two possible modes of alkyne formation are depicted in equation 97[454]. Reaction of diphenylcyclopropenone with singlet oxygen or potassium permanganate gives[454] desoxybenzoin.

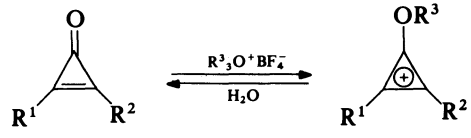


(97)

R^1 = Ph, *t*-Bu; R^1R^1 = -$(CH_2)_5$-; R^2 = *m*-ClC_6H_4

4. Reaction with electrophiles

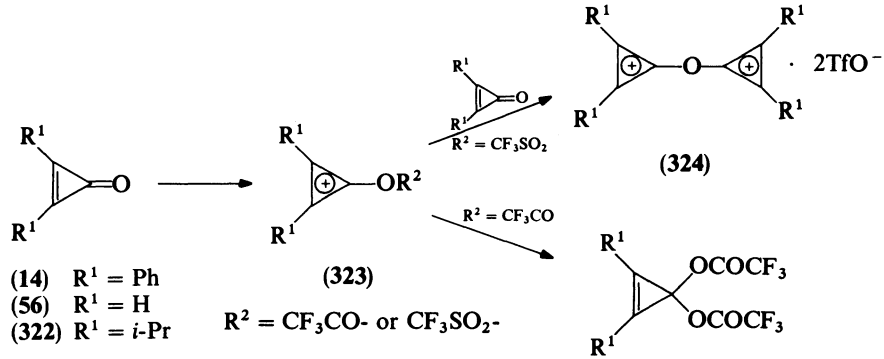
In accord with the relatively high basicity of cyclopropenone ($pK_b = -5.2 \pm 0.3$) and its derivatives (substituents at C(1) and C(2) increase the basicity; alkyl more so than phenyl), these compounds are protonated in strong acids to give the corresponding hydroxycyclopropenium salts e.g. **321** ($R^3 = H$)[114,455]. The salts generated in this manner can be captured with various nucleophiles, including thiocarboxylic acids, and such processes have been used to convert cyclopropenones into their thio analogues[456]. Cyclopropenone *O*-alkylation can be effected by treatment with trialkyloxonium tetrafluoroborates and the cations produced are easily hydrolysed to the starting enone[114,457]. Reaction of



(321)

$R^1 = R^2 = Ph$, p-MeC_6H_4; $R^1 = H$, $R^2 = Ph$; $R^3 = H$, Me, Et

cyclopropenone with trifluoroacetic anhydride provides acetal **325** the formation of which involves the ion **323** ($R^2 = CF_3CO$)[449]. In a related process treatment of **56** or its diphenyl analogue with triflic anhydride yields the stable but hygroscopic dication ether salts **324** via the monocation **323** ($R^2 = CF_3SO_2$)[458]. The reaction of cyclopropenones, e.g. **14**, with



(14) R^1 = Ph
(56) R^1 = H
(322) R^1 = *i*-Pr

(323)

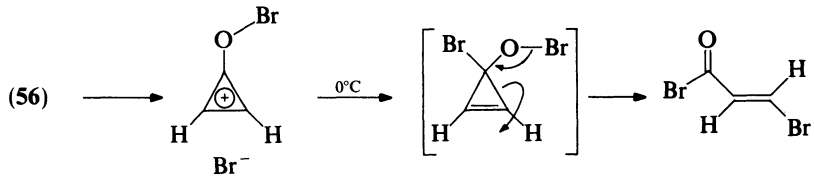
$R^2 = CF_3CO$- or CF_3SO_2-

(324)

(325)

thionyl chloride gives the corresponding gem-dichlorocyclopropene and an oxygenated cyclopropenium ion intermediate is likely[459].

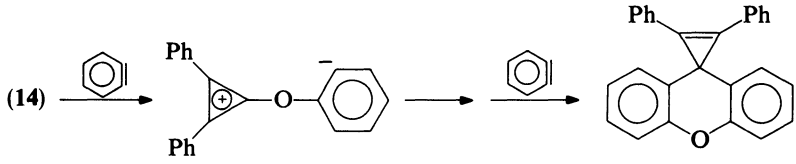
Low temperature bromination of cyclopropenone gives a 1:1 adduct, thought to be salt **326,** which is converted[449] into **327** on warming to 0°C.



(326)

(327)

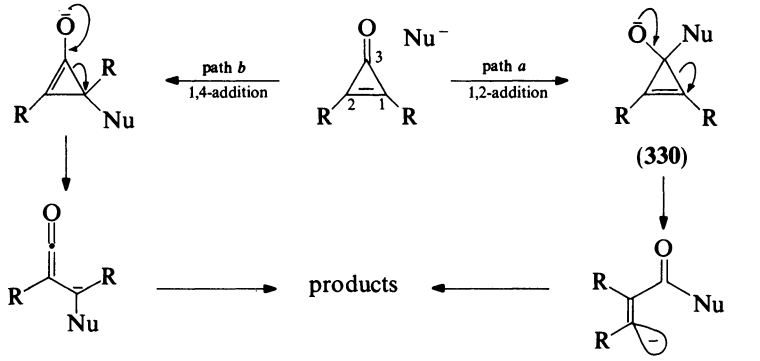
The reaction of isocyanates and ketenes with diarylcyclopropenones[460] involves initial electrophilic attack at the carbonyl oxygen of the enone and cyclopropenonimines and triafulvenes are the ultimate products of reaction (Sections II.F and II.G). The formation of the 1:2 adduct **329** from **14** and dehydrobenzene is rationalized by a complex path which, however, involves initial electrophilic attack on the cyclopropenone oxygen atom to give zwitterion **328** (equation 98)[461].



(328) (329) (98)

5. *Reaction with nucleophiles*

The behaviour of cyclopropenones with nucleophiles has been extensively studied[114a,b]. The outcome of a large number of such reactions can be explained by two generalized pathways as outlined in equation 99. Path *a* proceeds by nucleophilic attack at C(3) to give

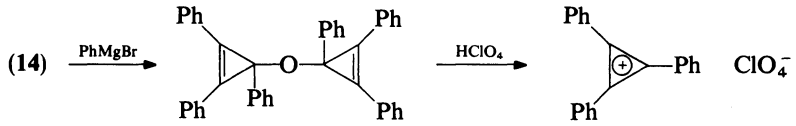


(330) (99)

(331) (332)

the vinyl anion **332** which reacts further to give cyclic and/or acyclic products depending upon the particular nucleophile employed. The hydroxide ion promoted conversion of cyclopropenones into acrylic acids by protonation of **332** has analogy to the Favorskii reaction and is the most studied of these 1,2-addition processes. The regiochemical outcome of the reaction depends upon both steric and electronic factors[434,442,444,445,455,462]. Certain malononitrile, ethyl cyanoacetate, alkoxide and thiophenolate anions behave similarly and give the requisite acrylic acid derivatives or tautomers thereof[442,463]. Moreover, the reaction of various carboxylates, amides, amines (but not ammonia, see below) thioamides, ynamines, pyridines and β-acylenamines give products which are rationalized in terms of an initial 1,2-addition[450,464].

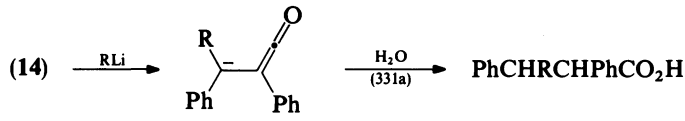
Under certain circumstances the initially produced anion **330** (equation 99) reacts further leaving the three-membered ring intact[465]. For example, phenylmagnesium bromide reacts with **14** to give the ether **333** which cleaves with acid to salt **19**. Where the



(333) (19)

nucleophile is an active methylene compound, protonation and dehydration of intermediate **330**[457,463] can occur to give a methylenecyclopropene (Section II.G).

The reaction of phenyl and benzyl lithium with **14** results in 1,4-addition (path *b*, equation 99) and gives rise to the ketene anion **331a**. Hydrolysis of this intermediate

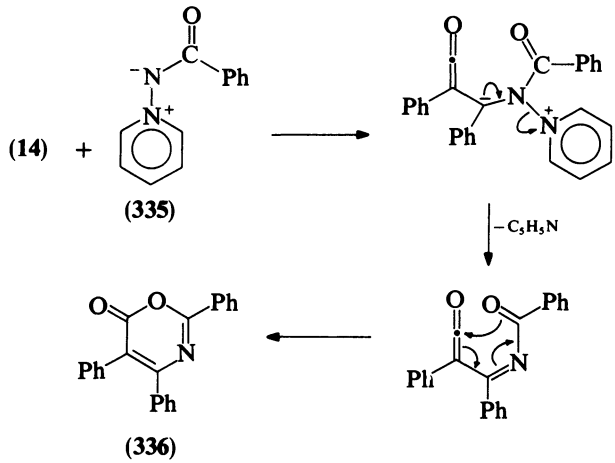


(331) **(334)**

a: R = Ph or $PhCH_2$
b: R = Ph_3P^+

gives[466] acid **334**. The isolation of ylides, e.g. **331b**, from reaction of some cyclopropenones with triphenylphosphine confirms the 1,4-addition process[467].

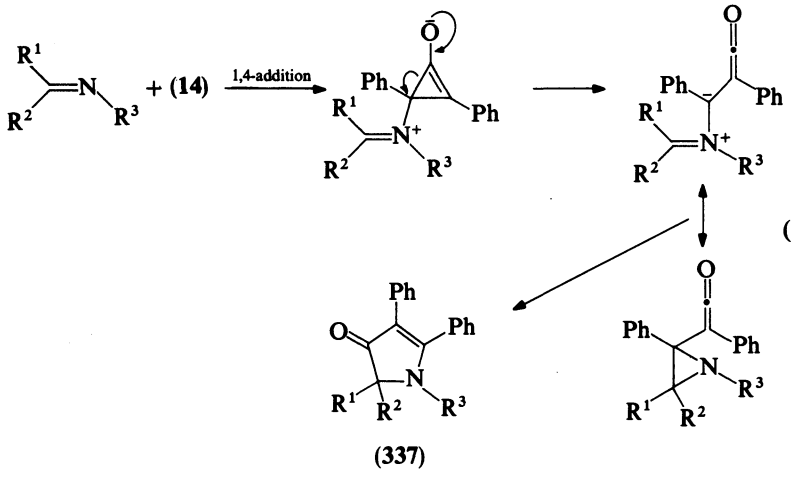
Certain ylides react with arylcyclopropenones via 1,4-addition to give α-pyrone and its heterocyclic derivatives[468]; the formation of the 1,3-oxazin-6-one **336** from reaction of the pyridine-*N*-imine **335** with **14** is representative[469]. Pyrimidones, pyridines and related

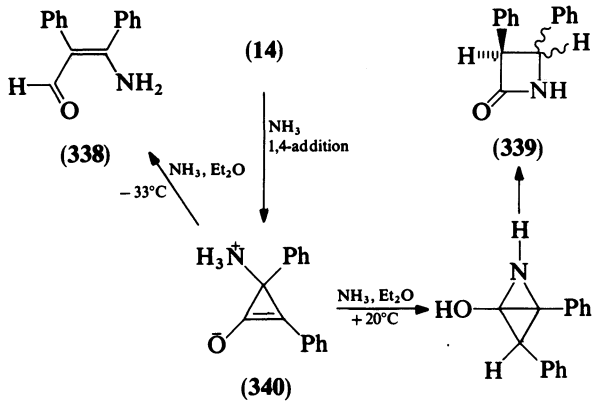


compounds are produced analogously from reaction of **14** with amidoximes, 1-azirenes, isoxazoles, selenoamides and certain guanidines[470].

The reaction of a wide range of imines and other compounds containing the C=N moiety with **14** leads[471] to the formation of azacyclopentenones, e.g. **337** (equation 100). Certain of the product heterocycles undergo oxidative dimerization[472]. Moreover, related five-membered ring systems result from analogous reactions of **14** with 1-(1′-pyrrolidinyl) acenaphthylene[473] and thiazoline-5-thiones[474].

Ammonia reacts with **14** to yield the enamine **338** at low (−33°C) temperature, but gives a mixture of the diphenylazetidinones **339** under ambient conditions; both products result from zwitterion **340**. With methylamine, **14** gives an azetidine at either temperature, whilst with aziridine ring-opening occurs[475]. *N*-Arylsulphimides and *N*-unsubstituted sulphoximines react with **14** by a 1,4-addition process to give ring-cleaved products[476].



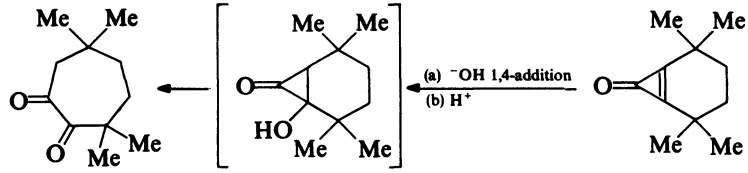


In some cases nucleophiles attack cyclopropenones in competing 1,2- and 1,4-addition processes[477]. Thus, treatment of the strained cyclopropenone **342** with sodium hydroxide gives the diketone **341** and the α,β-unsaturated acid **343** (equation 101, next page).

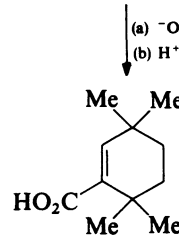
At low temperatures arylcyclopropenones condense with enamines by 1,2-addition to give[478] the 2-azoniabicyclo[3.1.0]hex-3-en-3-olates **344**, which isomerize on heating to penta-2,4-dienamides **348**. In an overall sense these products arise from insertion of the cyclopropenone three carbon unit into the C–N bond of the enamine and at elevated temperatures compounds **344** are not isolated. In certain instances, β-aminoenones **345**, ω-aminocyclopentenones **347** and cyclopentenones **346** (next page) also ensue[478]. Ketene acetals behave in a similar manner to enamines[478].

6. *Cycloaddition reactions of cyclopropenones*

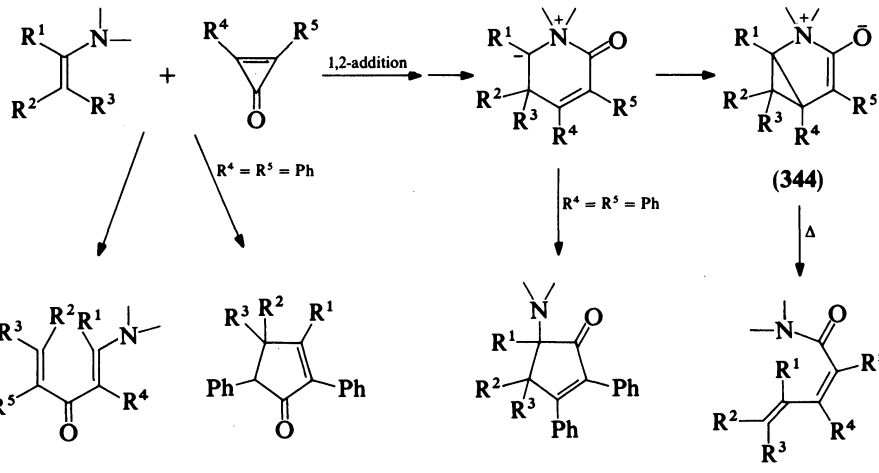
Cyclopropenones behave as olefinic 2π components for dipolar reagents ([2+3] cycloadditions) and dienes ([2+4] cycloadditions). Of the 1,3 dipoles various diazoalkanes add to diphenylcyclopropenone (**14**) to give bicycle **349** which fragments to



(341) (342) (101)



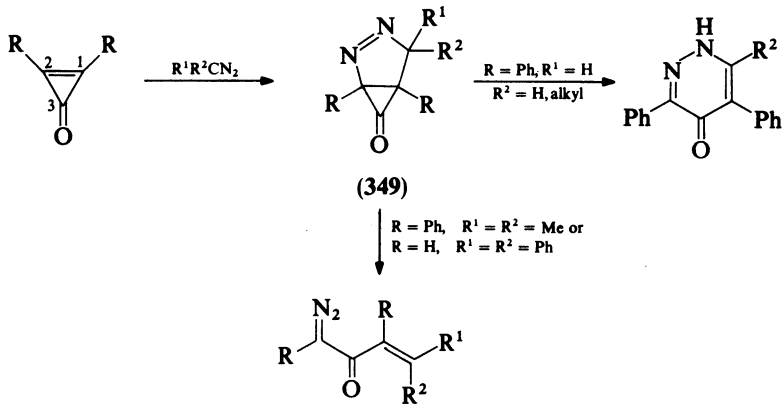
(343)



(345) (346) (347) (344) (348)

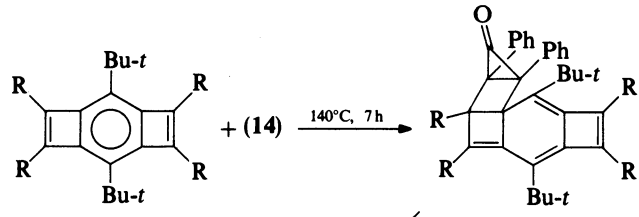
ring-expanded or ring-cleaved products depending upon the nature of the diazoalkane substituents[114, 116, 279, 444, 479] (equation 102). Analogous reactivity is shown by pyridinium dicyanomethylide[480], certain 3a,6a-diazopentalenes[481] and aziridines which function as precursors to azomethine ylides[482].

The Diels–Alder reactivity of the cyclopropenones has been examined theoretically[483] and is well established[114] but not extensive. The initial [2 + 4] adducts are rarely isolated but react further by cycloreversion[114c], elimination[449, 483], solvent addition[114c, 449], or isomerization processes[114c, 449, 484]. For example, **14** reacts with the annelated cyclobutadiene **350** in an initial [2 + 4] manner to give **351** which affords an isolable quadricyclone



(349)

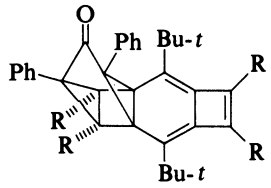
(102)



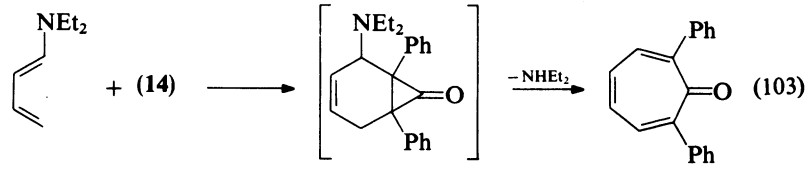
(350)

R = Ph or *p*-MeC_6H_4

(351)



derivative by a non-concerted $[_{\pi}2_s + _{\sigma}2_s]$ process[484]. Similarly, **14** adds to dienamine **352** to give the tropone **353** (equation 103)[483]but with diphenylisobenzofuran the actual Diels–Alder adduct is isolable[449].



(103)

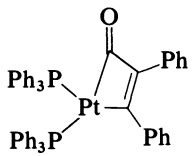
(352)

(353)

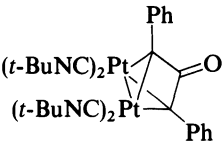
7. Organometallic derivatives of cyclopropenones

Until recently the isolation of organometallic complexes of cyclopropenones in which the ring is intact proved difficult[485] because of ring-opening (a process subjected to

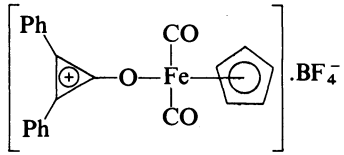
theoretical study[486]) and/or the formation of complexes too unstable, or too insoluble, for characterization. As noted earlier (Section VI.B.1), a variety of metal carbonyl compounds effect the decarbonylation of cyclopropenones and consequently alkyne rather than cyclopropenone complexes are often isolated. Octacarbonyldicobalt and **14** form an unstable complex formulated as $[(\text{diphenylcyclopropenone})_6\ Co][Co(CO)_4]_2$ which generates hexacarbonyl(diphenylacetylene)dicobalt upon warming[446]; the mode of bonding between the cyclopropenone and the cobalt is not known. The reactions of **14** with various organoplatinium complexes give metallacycles, e.g. **354**, by insertion of the metal into a σ bond of the three-membered ring[487]. In contrast, the dinuclear complex **355** is obtained from **14** by C(1)–C(2) bond cleavage with $Pt_3(t\text{-BuNC})_6$[488]. The intact



(354)



(355)

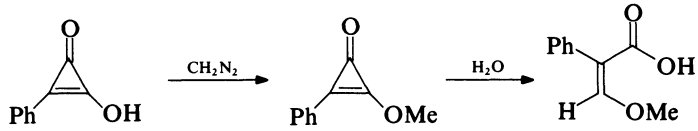


(356)

complexes of **14** and Sn(IV)[489] and Fe (II)[485, 490] systems, e.g. **356**, have been isolated and coordination occurs through the exocyclic carbonyl oxygen atom. Diferrocenylcyclopropenone has been prepared[491].

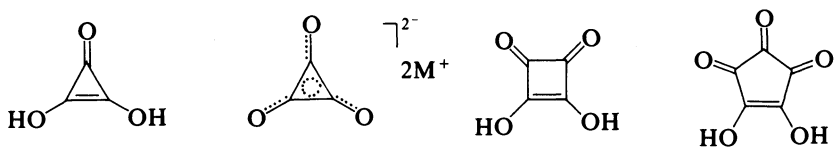
C. Hydroxycyclopropenones

Like its vinylogue tropolone, hydroxycyclopropenone ($pK_a \sim 2.0$) is alkylated with diazoalkanes. The derived ethers, e.g. **357**, are hydrolysed in aqueous acetone to the acrylic acid, e.g. **358**[492].



(357) (358)

Deltic acid (**70**) is an air-stable, easily prepared (Section II.F) solid which is readily bismethylated[493]. Its derived dianion (**359**) represents the first member of the potentially aromatic cyclic oxocarbons described by the formula $C_nO_n^{2-}$ [494]. Calculations suggest that



(70) (359) (360) (361)

M = Li, Na, K

359 is aromatic (and diatropic) although higher members of the series may not be[495]. The infrared and Raman spectra of the salts of **359** confirm D_{3h} symmetry and indicate

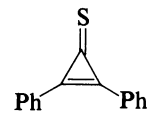
increased C–C and decreased C–O bond orders compared[496] to its higher homologues. However, deltic acid is a significantly weaker acid ($pK_1 \simeq 2.6$, $pK_2 = 6.0$) in both dissociations than homologues **360** ($pK_1 \sim 0.5$, $pK_2 \sim 3.5$) and **361**. Enthalpy and entropy factors probably affect the pK_as of deltic acid[497].

D. Heteroatom Derivatives of Cyclopropenones

1. Cyclopropenethiones

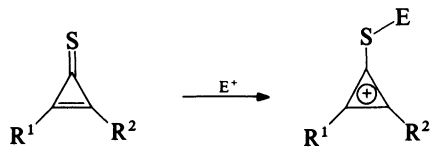
Cyclopropenethiones are readily available (Section II.F) and in many respects their chemistry is similar to that of the enones. Whilst X-ray results[498] from diphenylcyclopropenethione (**362**) imply little contribution of the dipolar form, MO calculations[424, 499] strongly support the aromatic charge-separated system with a π electron density on sulphur higher than on the oxygen in cyclopropenone. The infrared and Raman spectra of **362** and its perdeuterio derivative have been obtained and the bands assigned by normal coordinate analysis. When compared to the spectrum of diphenylcyclopropenone (**14**) shifts to 1786 and 1352 cm^{-1} are found[500].

Thermolysis of thione **362** contrasts with its oxygen analogue **14** in giving only small quantities of diphenylacetylene; the mass spectrum of **362**, unlike that of **14**, shows a molecular ion peak. The photochemistry of **362** is complex; depending upon the conditions employed diphenylacetylene, tetraphenylthiophenothiophene, diphenylcyclopropenethione dimers, thioacrylates and thietes or mixtures thereof are formed[501]. Oxidation of **362** with lead tetraacetate delivers **14** and the electrochemical reduction has



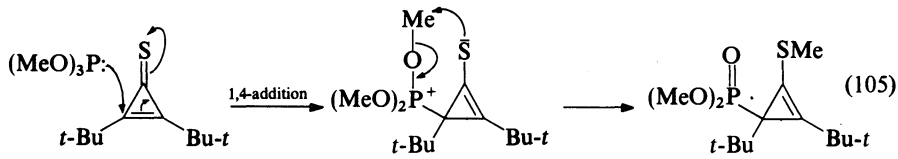
(362)

been studied ($E_{\frac{1}{2}}^{1}/V = -1.40$)[502]. Cyclopropenethiones also react with a variety of electrophiles at sulphur to give the corresponding cyclopropenium ion (equation 104)



(104)

which can be captured by nucleophiles[503]. Moreover, cyclopropenethiones react with a wide range of nucleophiles to give ring-cleaved products by 1,2-[504] or 1,4-[473, 480, 505] addition processes; occasionally the ring remains intact (equation 105)[506].



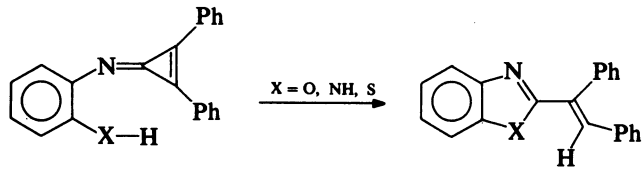
(105)

Organometallic derivatives of cyclopropenethiones containing the intact[507, 509] and the ring-cleaved carbocycle[508, 509] (scission of the C–C single bond) are known. In the former systems coordination is through the sulphur atom.

2. Cyclopropenimines

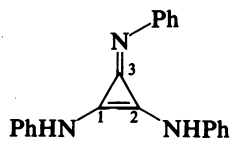
Although the [2 + 1]cycloaddition of isonitriles to the activated triple bond of ynamines and certain cycloalkynes provides a useful route to some cyclopropenimines[122], the equivalent cycloreversion process is of minor significance in the thermolysis of these compounds; dimerization and ring-cleavage processes predominate[114, 510]. The photolysis of diphenylcyclopropenimines gives phenanthracene derivatives[114, 511].

N-Arylcyclopropenimines **363** having a nucleophilic moiety at the *o*-position of the aromatic ring can isomerize to the five-membered heterocycles **364** in a process reminiscent of the conversion of cyclopropenones into acrylic acid derivatives (Section VI.B.5)[512].

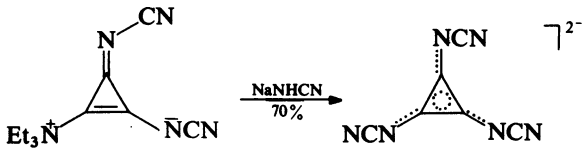


(363) **(364)**

The unstable imine **73a** is the first aza analogue of deltic acid[131]. A single carbon resonance (δ 115.0) for C(1)C(2)C(3) indicates rapid prototropic shift between the three nitrogen atoms. The deltate dianion equivalent is available from the zwitterion **80**[133].



(73a)

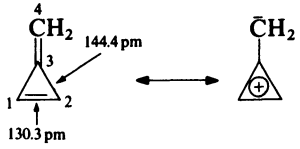


(80)

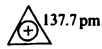
VII. METHYLENECYCLOPROPENES

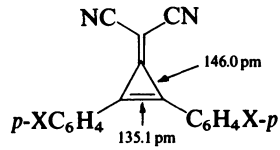
A. Physical and Theoretical Aspects

Methylenecyclopropene (triafulvene) is the simplest member of the cross-conjugated, non-alternant, hydrocarbon family known as the fulvenes. Strong polarization of the π-system might be expected for such a structure and extensive efforts[114, 141] have been made to assess the contribution that the dipolar form **85b** makes to the resonance hybrid **85**. The stability of the methylenecyclopropenes is markedly enhanced by electron-withdrawing groups at C(4) which stabilize the dipolar form. Thus, while **365** is stable[114] the parent **85** is



(85a) (85b)





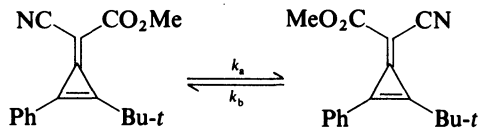
(365)

a: X = H
b: X = F

not; dilute pentane solutions of **85** show[147] a half-life of approximately 20 h at − 78°C. Consequently, the majority of experimental studies have been restricted to such stabilized derivatives and this area has been reviewed[114a,c].

MINDO/2 and MINDO/3 calculations give the heat of formation (at 25°C) of **85** as 259.2 and 338.6 kJ mol^{-1} respectively[513] and other MO calculations suggest only minor resonance stabilization ($< 1\beta$)[114a]. However, an *ab initio* treatment gives a geometry of the three-membered ring close to the STO-3G structure of the cyclopropenyl cation[514]. Calculated dipole moments of 2.08 and 1.33 D for **85** have been reported[514,515].

Structure analyses of the triafulvenes[114,426,516], e.g. **365**, show bond lengths in the three-membered ring to be intermediate in length to those expected for the fully localized and delocalized structures and suggest a significant dipolar contribution. Despite the similar electron-withdrawing capacities of oxygen and the $C(CN)_2$ moiety, CNDO/2 calculations based on such structural data suggest a higher positive charge on the C(1) C(2) atoms and the phenyl groups in **365a** than in diphenylcyclopropenone[426]. This conclusion is supported by ^{19}F-NMR measurements of the bis-*p*-fluorophenyl species **365b**[114a]. The low temperature ^{1}H-NMR spectrum of the parent **85**[147] (Section II.G) is interpreted in terms of a significant contribution from the dipolar species **85b**. A temperature dependence in the NMR spectra of asymmetrically substituted triafulvenes implies single character in the exocyclic bond and resultant rotation. Thus, fulvenes such as **366** crystallize in one configurational form and equilibrate in solution with the rotamer; various parameters for these interconversions have been determined (equation 106)[114a,517].

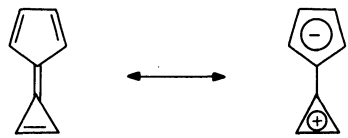


(106)

(366)

$k_a = 9.25 \times 10^{-5}$ s^{-1}; $\Delta G_a = 120.5$ kJ mol^{-1} $\tau_{1/2}^{100°} = 66.5$ min.
$k_b = 8.12 \times 10^{-5}$ s^{-1}; $\Delta G_b = 121.0$ kJ mol^{-1}

Triafulvene ring systems capable of extended delocalization of charge (e.g. calicene **367**) give spectral data fully compatible with highly dipolar character[141,518] and many of these compounds possess significant dipole moments[114a].



(367)

The methylenecyclopropenes display characteristic infrared bands between 1810–1880 and 1510–1550 cm^{-1} and these absorptions undoubtedly result from strong coupling between the two double bonds; however, no detailed infrared or Raman analysis of triafulvenes has been undertaken[114a]. Methylenecyclopropene itself displays[147] bands at 1770 and 1519 cm^{-1}.

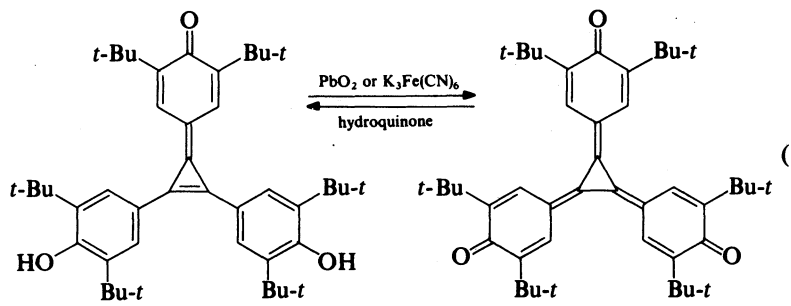
The ultraviolet spectrum of methylenecyclopropene[147] displays low intensity bands at 309 and 242 nm and a strong band at 206 nm. The first solvent-dependent band is identified[519] with a $^1B_2$ ($\pi \rightarrow \pi^*_1$ internal charge transfer) transition whilst the intense short wavelength band shows only weak solvent dependence and arises from the $^1A_1$ ($\pi \rightarrow \pi^*_2$) transition. The 242 nm band is assumed to result from a $^1B_1$ ($\pi_1 \rightarrow \sigma^*_2$) transition. An expected[519] second $^1B_1$ transition ($\sigma \rightarrow \pi^*_1$) is probably obscured by the tail of the 206 nm band.

The extensive mass spectral studies of the triafulvenes have been summarized[114a]. The radical cation of **85** is observed[147] in the mass spectrum of methylenecyclopropene and is the most stable $C_4H_4^{+\cdot}$ species[520]. By analogy with cyclopropenones fragment ions derived from cycloreversion to alkynes are often observed.

B. Chemical Reactivity

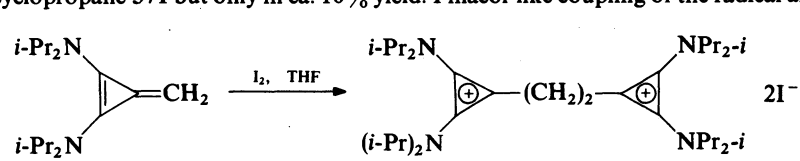
1. Oxidation and reduction processes

Many phenoxy-substituted fulvenes, e.g. **368**, are oxidized[149,151,521] to the corresponding highly coloured [3]radialenes. Reduction of the latter species can be effected with hydroquinone (equation 107). Oxidative cleavage[522] of some triafulvenes to allenes is



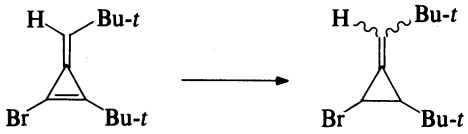
(368)

effected with molecular oxygen or ferric chloride and oxidative coupling of **369** by iodine is noted[523]. Hydrogenation of **370** over 5% rhodium on alumina delivers[144] the methylenecyclopropane **371** but only in ca. 10% yield. Pinacol-like coupling of the radical anion



(369)

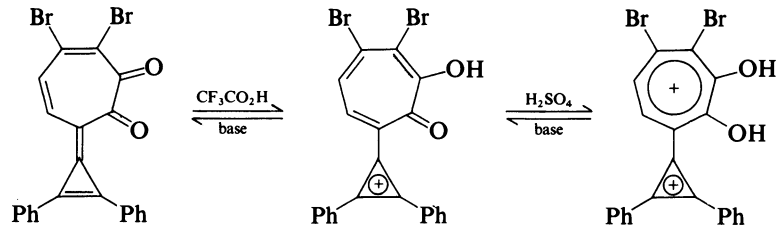
obtained from polarographic reduction of **365a** gives the corresponding 3,3′-bicyclopropenyl which aromatizes[524].



(370) (371)

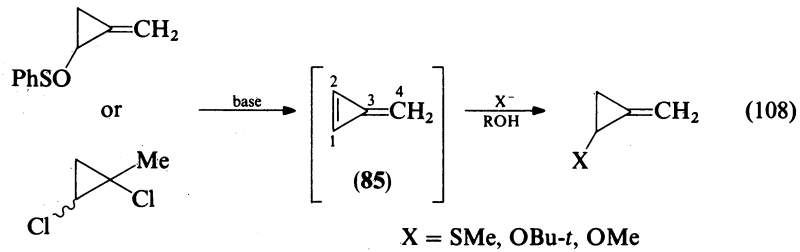
2. *Reactions with electrophiles and nucleophiles*

Protonation of the methylenecyclopropenes occurs to give the corresponding cyclopropenium ion as exemplified by **372** which can protonate further to the dication. Regeneration of **372** occurs with base[114c,525].



(372)

Nucleophiles attack the methylenecyclopropenes exclusively at the ring carbon atoms[114] and products from precursors to these compounds provide[145,526] strong evidence for the intermediacy of **85** (e.g. equation 108). The formation of a cycloprop-



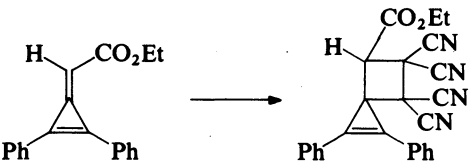
(108)

enone and an ynone from the hydrolysis of **370** (cf. equation 33, Section II.G) suggests[144] that nucleophilic attack occurs at C(1) and C(3). Enamines attack triafulvenes in a similar manner[114a,527].

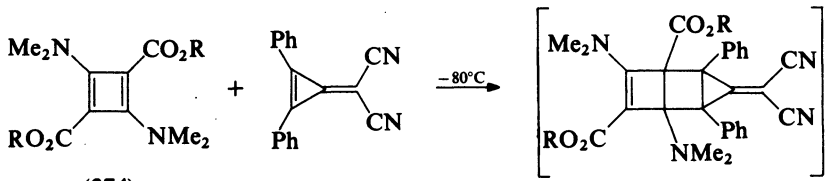
3. *Cycloaddition reactions*

a. [2+2] *Cycloadditions*

Tetracyanoethylene adds to the exocyclic double bond of **373** to give spirocyclic product[528], whilst the cyclobutadiene **374** adds to the endocyclic double bond of a variety of methylenecyclopropenes to give tricyclic [2+2] adducts, e.g. **375**, which rearrange[114a,529] to heptafulvenes, e.g. **376**.

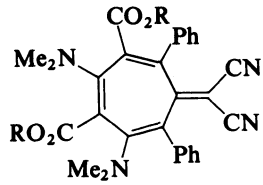


(373)



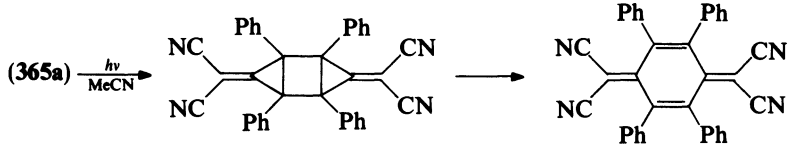
(374)

(375)



(376)

Photodimerization of **365a** gives the *p*-quinodimethane **378** by a [2+2] reaction across C(1)–C(2) and subsequent ring cleavage within dimer **377**[530]. The reaction of a



(377) (378)

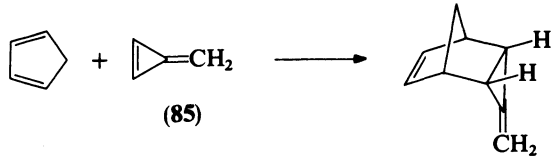
variety of methylenecyclopropenes with dimethyl acetylenedicarboxylate or maleic anhydride gives ring-expanded products by either initial [2+2] or [2+4] cycloadditions[531].

b. [2+4] *Cycloadditions*

Methylenecyclopropenes can function as the 2π addend in Diels–Alder cycloadditions, and it is only the endocyclic double bond that is involved (Section II.G); thus, reaction of **85** with cyclopentadiene affords *endo* adduct **379** (opposite) exclusively[114, 145, 526, 531].

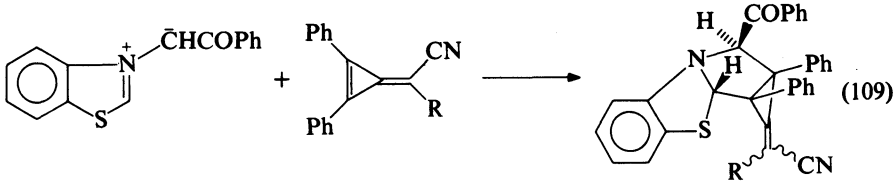
c. Dipolar [2+3] *cycloadditions.*

The mode of 1,3-dipolar cycloaddition of a methylenecyclopropene depends upon the nature of the dipole and the C(4) substituent of the fulvene[114a]. Normally, the initial



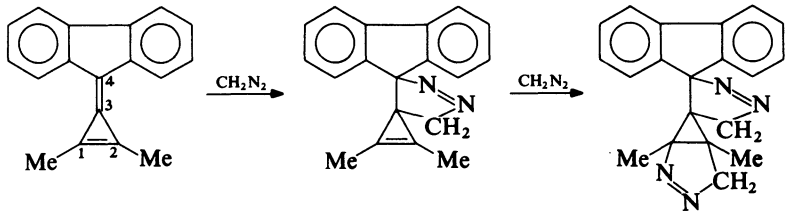
(85) (379)

adduct ring expands[532] but benzothiazolium *N*-phenacylide adds[533] to the endocyclic double bonds of certain methylenecyclopropenes to give primary adducts with *endo*-stereochemistry in good yields (equation 109). Dipolar addition to the endocyclic π bond



(109)

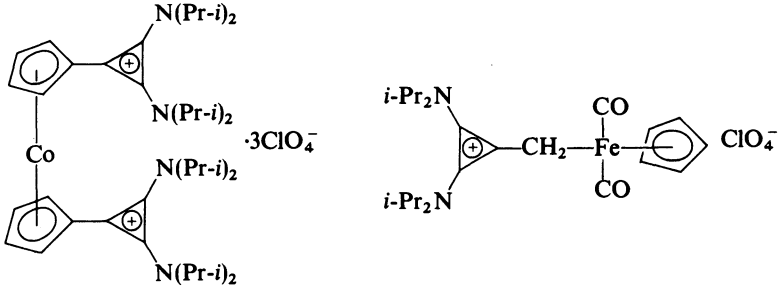
represents the favoured mode of reaction, but attack at the exocyclic double bond is known. Reaction of the calicene **380** with diazomethane gives the 2:1 adduct **381** which is thought[531] to arise from primary attack of the 1,3-dipole at the C(3)–C(4) bond.



(380) (381)

4. Organometallic derivatives

Metal complexes of the methylenecyclopropenes in which the ring skeleton is retained include[534] **382** and **383**; the negative end of the dipolar form of these molecules is bonded to the metal atom.



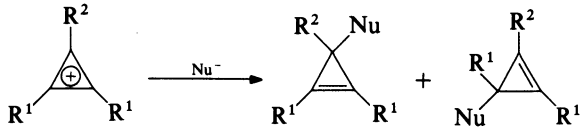
(382) (383)

VIII. THE CYCLOPROPENYL CATION, ANION, RADICAL AND CARBENE

A. The Cyclopropenyl Cation

Cyclopropenyl cations are readily available from the ionization of cyclopropenes carrying a suitable leaving group at C(3)[114c,535] (Section II.A) or by electrophilic attack on cyclopropenones (Section VI.B.4), cyclopropenethiones (Section VI.D.1), cyclopropenimines (Section VI.D.2) or triafulvenes (Section VII.B.2). The cation is the simplest Hückel aromatic species and is discussed in detail in Chapter 24.

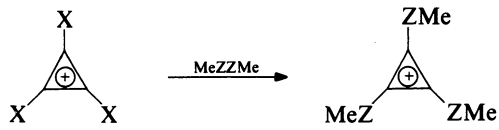
The single most important reaction of cyclopropenium ions involves their capture by nucleophiles[114c]. Such reactions give the corresponding cyclopropene which may survive the reaction conditions[114c,270,536], eliminate to yield a triafulvene (Section II.G), ionize to a new cyclopropenium ion[114c,537], or ring cleave[114c,538]. With unsymmetrically substituted cyclopropenium ions mixtures of cyclopropenes are often produced (equation 110) although regioselective processes are known[114c,459,538].



(110)

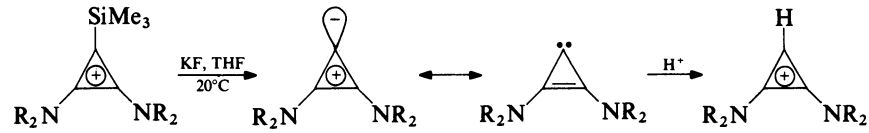
The conversion of one cyclopropenium ion into another, a substitution reaction, is gaining synthetic importance. Until recently, only nucleophilic substitution reactions of the nucleophilic addition–elimination type were known[537]. However, three other processes are now recognized. These processes are:

(1) four-centre exchanges[539,540]

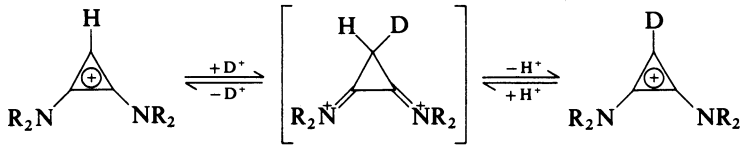


X = Cl, Br; Z = S, Se, Te

(2) elimination–additions proceeding via the cyclopropenylidene[541]



(3) electrophilic substitution[540,542]



The important influence of the counterion on many of these substitutions has been exploited synthetically[540].

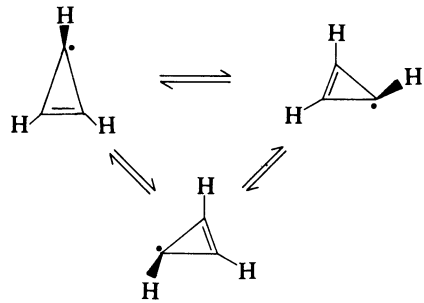
Reduction of the triphenylcyclopropenium cation with zinc, magnesium and chromium salts, or by electrolysis affords hexaphenyl 3,3'-bicyclopropenyl via the triphenylcyclopropenyl radical[114c]. With lithium aluminium hydride[114c] the triarylcyclopropenium ions are reduced to the corresponding triarylcyclopropene.

Benzocyclopropenium cations, generated from the gem-dihalogenocyclopropabenzenes, are very sensitive to moisture and are converted into benzoic acids[543]

B. The Cyclopropenyl Radical

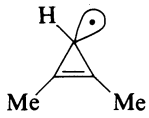
The parent cyclopropenyl radical is yet to be observed directly. Various theoretical studies[544,545] suggest that the highly symmetric D_{3h} form **384** is subject to Jahn–Teller distortion and is consequently much less stable than the low symmetry non-planar C_S σ radical equilibrium structure **385**. Three equivalent conformations are possible for **385** and these can interconvert ($\Delta H^{\ddagger}$ 12–30 kJ mol^{-1})[544,546] via a non-planar allylic transition state structure. Planar geometries are of much higher energy and play no significant role in

(384)

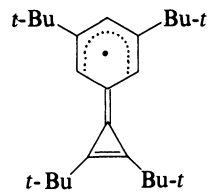


(385)

the dynamics of this system. Experimental studies support these arguments[546–548]. Thus, the trimethylcyclopropenyl radical is an equilibrating mixture of C_S species with the unpaired electron sited on each ring carbon atom in turn. In the dimethyl derivative **386**[547] the lone electron is preferentially located on the unsubstituted carbon atom.



(386)



(387)

An ESR study[548] of the 1,2-di-*t*-butyl-3-(3,5-di-*t*-butylphenyl)cyclopropenyl radical (**387**) shows that the unpaired electron is predominantly in the phenyl ring and forced away from the three-membered ring by a destabilizing interaction with the π electrons of the cyclopropenyl double bond. The cyclopropenyl radical may thus possess some antiaromatic character. An ion cyclotron double resonance bracketing experiment[549]

suggests that the heat of formation of the cyclopropenyl radical (439 ± 17 kJ mol^{-1}) is considerably higher than for the cyclopropyl (278 ± 11 kJ mol^{-1}) equivalent.

Trimethylcyclopropenyl radical, when generated by pulse radiolysis[550] from the correspondinng cyclopropenium cation, complexes with the cation and also dimerizes to hexamethylbenzene, possibly via the 3,3′-bicyclopropenyl.

C. The Cyclopropenyl Anion

The cyclopropenyl anion (**388**), the smallest possible Hückel 4π electron carbocycle, has often been regarded as the 'antiaromatic' prototype[551]. In contrast with earlier theoretical work[552], a very recent[553] *ab initio* study suggests that the singlet and triplet states of the anion are strongly distorted from planarity. The ground state is a 'A' singlet (C_s geometry) with one hydrogen atom strongly out of the plane and the other two hydrogens bent out of the plane in the opposite direction. The triplet cyclopropenyl anion is ca. 63 kJ mol^{-1} less stable than the singlet species, and also prefers non-planar geometries in order to reduce electron repulsion and relieve antiaromatic character. Despite these expected distortions, the generation of **388** appears to be energetically unfavourable. Calculations[554] support the replacement of a vinylic hydrogen rather than a methylene hydrogen of cyclopropene by lithium because of the development of antiaromatic character in the latter process. Such selectivity is noted experimentally[69,198–200,555]; thus treatment of cyclopropene with lithium, sodium, or potassium amide leads to the vinyl anion **389** which reacts with electrophiles to give 1-substituted cyclopropenes (Section IV.A.1).

(388) **(389)**

Electrochemical studies[556] provide cyclopropene C(3) pK_a values in the range 50–75 which emphasizes the thermodynamic instability of anion **388** and its derivatives. The observations[556,557] that 3-benzoyl- and 3-cyano-1,2-diphenylcyclopropenes undergo base-catalysed hydrogen–deuterium exchange much more slowly than their cyclopropane counterparts indicates that anion **388** and its derivatives are energetically disfavoured species. Additional support stems from the fact that bases do not abstract the C(3) hydrogen atom in tribenzoylcyclopropene but effect ring cleavage instead. In the light of such results, the ready formation of cyclopropabenzenyl anion (pK_a = 36) and its cyclopropa[*b*]naphthalene counterpart suggests extensive charge delocalization into the aromatic rings of these species[148,558].

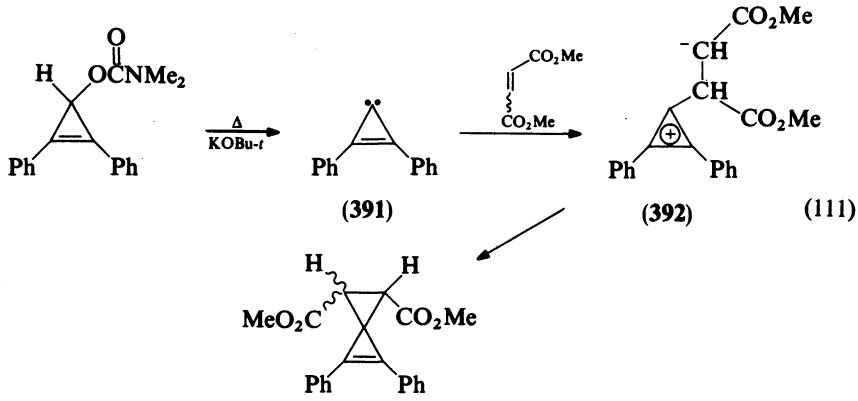
D. Cyclopropenylidene

In agreement with earlier theoretical work[559], non-empirical structure theory[560] predicts that cyclopropenylidene (**390**) has a singlet ground state ca. 290 kJ mol^{-1} below the lowest triplet. The expected high dipole moment (~ 3.40 D) suggests a significant contribution of

(390a) **(390b)**

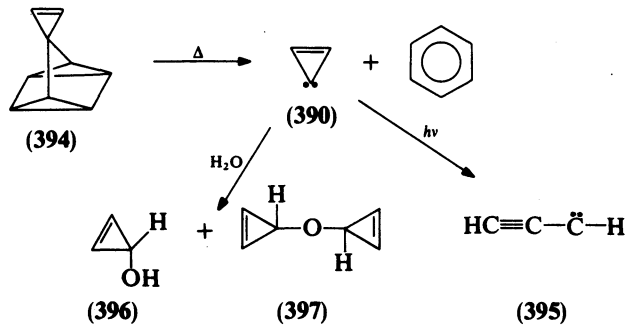
the 'onium anion **390b** to the resonance hybrid, and **390** is predicted to be a very nucleophilic carbene[559-561].

Diphenylcyclopropenylidene (**391**)[561] reacts with electrophilic olefins such as dimethyl fumarate and maleate only. The fact that the same spiropentene **393** (stereochemistry unknown) is isolated from reaction of **391** with both alkenes (equation 111) supports the intervention of zwitterion **392** and augments the concept of cyclopropenylidenes being very nucleophilic carbenes.



Bis-(dialkylamino)cyclopropenylidenes[562], prepared by deprotonation of the corresponding cyclopropenium ions, have been studied spectroscopically[562] and complexed with metal atoms[563]. (For indirect methods of preparation of cyclopropenylidene metal complexes, see Section V.A).

Parent cyclopropenylidene **390** has been generated recently[564] from flash thermolysis of the quadricyclane **394** and trapped in an argon matrix at 10 K. Compound **390** displays an infrared spectrum in accord with theory[17] and provides propynylidene **395** upon irradiation; reaction with water leads to insertion products **396** and **397**.



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CHAPTER **22**

Aminocyclopropanes

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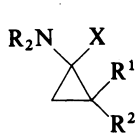
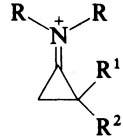
I. INTRODUCTION

Aminocyclopropanes (**1**) are typical representatives of the family of donor-substituted cyclopropanes. The combination of an amino moiety with the cyclopropane ring is not only of theoretical interest for possible donor–acceptor interactions, but is also the origin of an easy nucleophilic substitution of a group X in (**1**) or a ring-opening reaction. Intermediates **2** and **3** represent these two types of reactions; according to the sequence **1** → **3** an aminocyclopropane is to be regarded as a homoenamine species.



(**1**)



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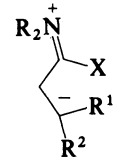
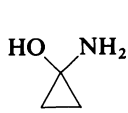


(**3**)

Some aminocyclopropanes show biochemical activities. In some cases this is due to reactions of the three-membered ring (e.g. inhibition of acetaldehyde dehydrogenase by **4**,

inhibition of monoamine oxidase by **5** and biosynthesis of ethylene from **6**). In other cases a cyclopropylamino moiety in an active substance is not essential for the activity, but its use instead of other alkylamino moieties may offer special advantages (e.g. herbicide **7**: R = *c*-C_3H_5, Outfox^R; R = Et, Gesaprim^R; R = *i*-Pr, Gesamil^R).



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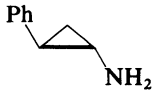

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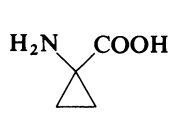

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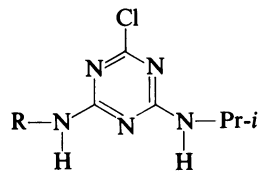


(7)

As a consequence of all these facts, interest in aminocyclopropane chemistry and biochemistry has strongly increased during the last 20 years. Thus between 1966 and 1985 aminocyclopropane derivatives were involved in over 3000 publications.

The following review covers especially the synthesis of aminocyclopropanes; it deals with compounds in which a NR^1R^2 moiety ($R^1R^2 \neq$ heteroatom) is directly bonded to the three-membered ring. Cyclopropanes with other nitrogen functional groups are not included. Literature was considered until the end of 1984; the text was supplemented in October 1985. A very short review on aminocyclopropane chemistry appeared in 1974 by Gibson and DePuy[1]; Wasserman and coworkers surveyed some aminocyclopropane compounds derived from cyclopropanones[2].

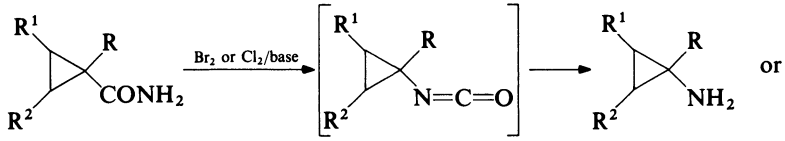
II. PREPARATION

A. Introduction of an Amino Function into a Cyclopropane

1. Introduction by cyclopropyl migration

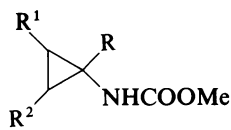
The well known Hofmann[2–35], Curtius[16–21, 24, 25, 31, 32, 35–174] and Lossen[17–19, 22, 31, 32, 175] degradation of the corresponding acid derivatives provides an easy access to aminocyclopropanes.

For the Hofmann degradation a cyclopropanecarboxamide (**8**) is treated with bromine, chlorine or hypochlorite in an aqueous hydroxide- or methanolic methoxide solution (equation 1). By this reaction Kishner prepared the first cyclopropylamine in 1902[3].



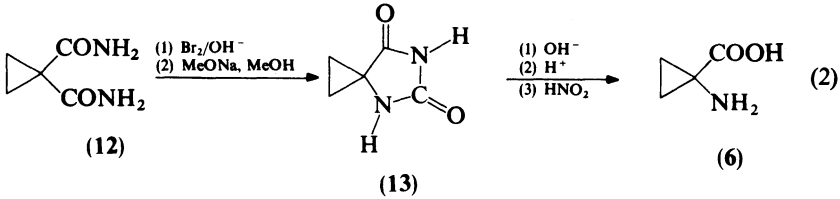
(8) (9) (10)

(1)



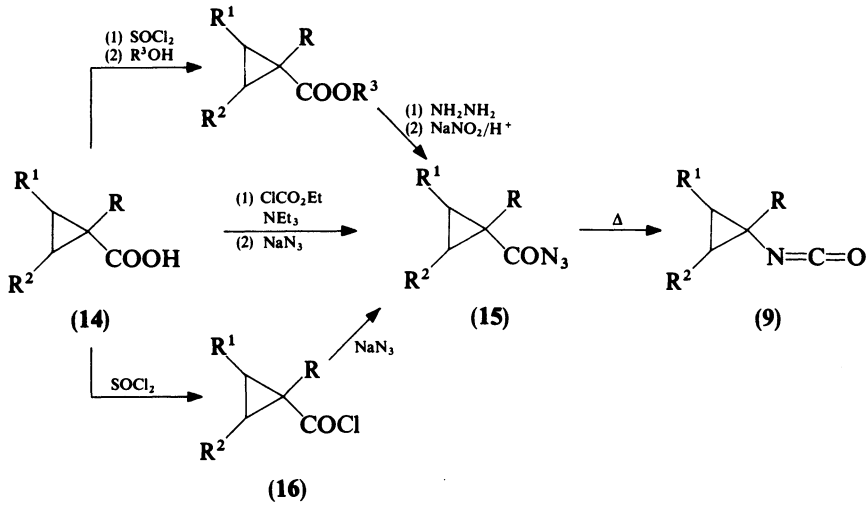
(11)

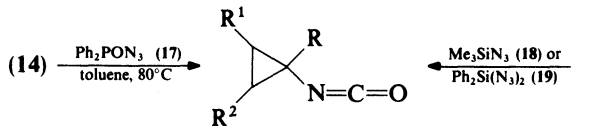
Today, the Hofmann degradation is also the basis for the simplest preparation of cyclopropylamine. The total yield of this synthesis starting from butyrolactone via cyclopropanecarboxylic acid is reported to be about 80%[15]. A ^{15}N-labelled cyclopropylamine was conveniently synthesized from the ^{15}N-amide[28]. From cyclopropane biscarboxamide (**12**) hydantoin (**13**) was obtained by a monodegradation step; **13** was hydrolyzed to aminocyclopropane carboxylic acid (**6**) (equation 2)[5–9]. Cyclopropane 1,2-biscarboxamide gave cyclothymine upon Hoffmann degradation[9a]. In a modified Hoffmann degradation giving lower yields, lead tetraacetate was also used as an oxidizing agent[30].



(12) (13) (6) (2)

Numerous aminocyclopropanes have been prepared by the Curtius degradation (Scheme 1). The acyl azides (**15**) were obtained in many cases from the acid chloride (**16**) and sodium azide either in an organic solvent ('Dry Sodium Azide Procedure')[42] or in water ('Wet Sodium Azide Procedure')[42]. A modified preparation was reported by





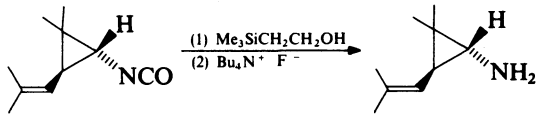
(9)

SCHEME 1

Weinstock[40,41]: reaction of NaN_3 with the mixture of the acid (**14**) and ethyl chloroformate instead of the acid chloride prevented isomerization of the cyclopropanecarboxylic acid chloride (**16**, R = H) which occasionally occurred with the former procedures. No isomerizations were reported when the azide (**15**) was prepared via the hydrazide from the ester.

The rearrangement of **15** to **9** was performed in most cases in refluxing benzene or toluene; irradiation also effected the dinitrogen extrusion[123]. The use of the silyl azides (**18**)[90,119] or **19**[90] allowed the preparation of **9** or the corresponding aminocyclopropane in a one pot procedure starting from the acid chloride or acid anhydride. A cyclopropyl isocyanate (**9**) also could be obtained directly from the carboxylic acid, triethylamine and diphenylphosphoryl azide (**17**)[161].

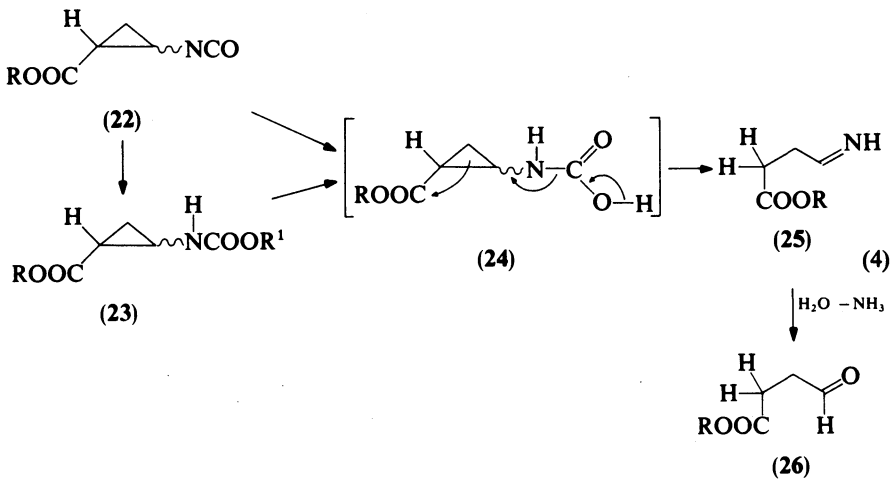
The isocyanates (**9**) were transformed into amino derivatives by standard reactions. Acid-sensitive aminocyclopropanes were obtained preferentially from benzyl[73,111,114]-, β-naphthyl[53,112]- or trifluorethyl-urethanes[42] which were cleaved by hydrogen, EtSNa/DMF or alkaline hydrolysis. The hydrazinolysis of phthalimido compounds obtained from the urethane and phthalic anhydride also was useful[57]. Trimethylsilylethanol proved to be advantageous for the isocyanate–amine conversion; the resulting urethanes gave amines upon addition of $Bu_4N^+ F^-$ [161] (e.g. synthesis of amine (**21**) from *trans*-crysanthemic acid via isocyanate (**20**)[161], equation 3). Contrarily to

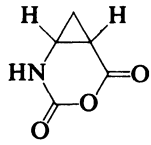


(3)

(**20**) (**21**) 79% yield[101]

trans-vinylcyclopropyl isocyanates, e.g. **20**, the corresponding *cis*-vinylcyclopropyl isocyanates generated by a Curtius degradation underwent a rapid 3,3-sigmatropic rearrangement to give dihydroazepinone derivatives[174,176,177]. Hydrolysis of β-acyl-substituted cyclopropyl isocyanates (**22**) or urethanes (**23**) caused the formation of ring-opened products (**26**)[82,94] or polymeric material[79] (equation 4). Ring-opening of the three-membered ring also was reported in a polycondensation reaction of cyclopropane (**27**)[91]

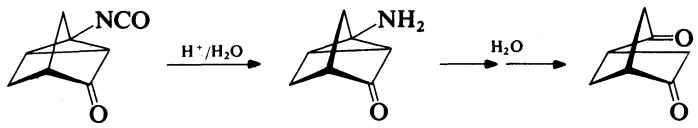




(5)

(27)

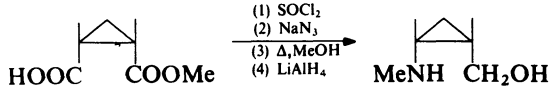
(equation 5). A ring cleavage was observed with the tricyclic isocyanate (**28**)[155] too; however, in this case **29** could be obtained by careful hydrolysis (equation 6)[155].



(6)

(**28**) (**29**) (**30**)

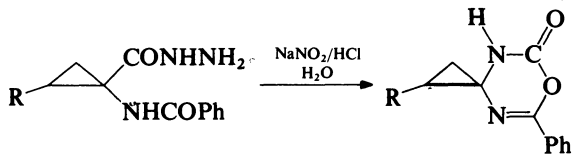
Simultaneous removal of the acceptor effect of the 2-substituent during *N*-acyl cleavage prohibited ring-opening, e.g. this allowed the preparation of **32** from **31** (equation 7)[82].



(7)

(**31**) (**32**)

1,1-Diamino-substituted cyclopropanes also could be synthesized from suitable precursors, e.g. preparation of **34** from **33**[98] (equation 8).

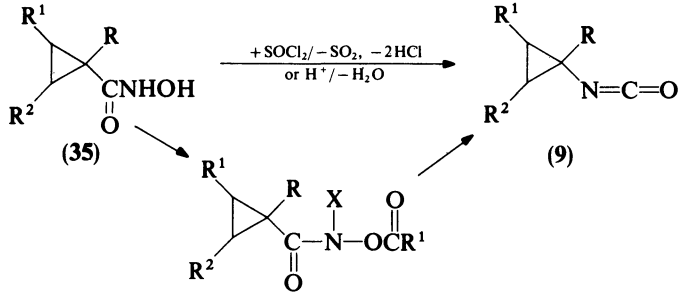


(8)

(**33**) (**34**)

The Lossen degradation was only rarely applied in the synthesis of aminocyclopropanes. **9** was obtained from **35** by treating with acid or thionyl chloride or by heating the acyl derivatives **36** (equation 9). Especially the potassium salts of **36** required lower temperatures for decomposition than the corresponding sodium or silver salts[175].

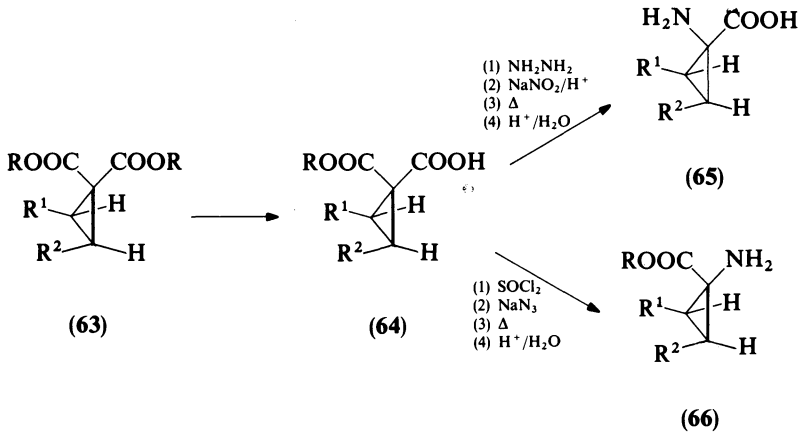
The acyl azide → isocyanate rearrangement is known to proceed stereospecifically with retention of both optical and geometrical (*cis–trans*, *endo–exo*) configuration. Thus, optically active aminocyclopropanes were obtained from optically active cyclopropane carboxylic acid derivatives[44, 50, 68, 87, 105, 143]. A lot of *exo*-amiobicyclo[n.1.0]alkanes or -alkenes have been synthesized from the corresponding *exo*-acid derivatives, which are easily prepared from cycloalkenes and ethyl diazoacetate. Such or other reaction sequences were described for the preparation of aminobicyclo[n.1.0]hexane[17–19, 24, 42, 58, 120, 172], -hexene[120, 168], -heptane[17, 18, 24, 42, 45–47, 60, 110], -heptene[60, 101, 109, 123, 145, 146, 150], -octane[17–19, 24], -octene[107, 150], -octadiene[77, 78, 108], -nonane[16–19, 24, 141], -nonene[141, 150], -nonatriene[134], -decane[17, 18], -undecane[150] and tridecane[150] (oxa- or



(9)

dioxabicyclo[n.1.0]alkane systems see Refs 66, 121, 136, 137, tri- and polycyclic systems see Refs 11, 21, 22, 42, 56, 65, 96, 97, 99, 103, 117, 121, 124, 138, 139, 147, 152–155). In some cases the accessibility of both diastereomers of a cyclopropane carboxylic acid allowed the preparation of the two diastereomerically pure amines; typical examples are shown in Table 1.

An interesting, highly selective approach to both diastereomers of some aminocyclopropanes started with diesters of type **63** or **67**. Saponification of **63** took place preferentially at the sterically less hindered *trans*- or *exo*-position (for references see Table 1). The free acid moiety in **64** could be transformed into an amino compound (**66**) via the carboxylic azide. Thereby, the ester carboxyl remained unaffected. On the other hand, the ester function of **64** could be converted into the amine (**65**) via the hydrazide without affecting the acid function (equation 10). Decarboxylation of **64** followed by ester amine

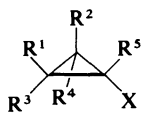


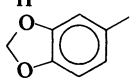
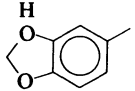
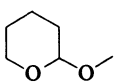
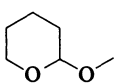
(10)

transformation was applied to the preparation of *endo*-aminobicycloalkanes **52** and **54** in Table 1. The stereoselective synthesis with **67** was based on the formation of the amide (**68**) or alternatively the ester (**69**)[35] (equation 11); a part of this sequence was also realized with **63**, e.g. synthesis of coronamic acid from **63** (R^1 = H, R^2 = Et, R = Me) or its methyl analog from **63** (R^1 = H, R = R^2 = Me)[27, 34].

Preparation of diaminocyclopropanes **70** and **71** by Curtius degradation was easy for the *trans*-derivative **70**[49, 54, 55, 57, 64, 104, 142] (enantiomers of **70**[142]). The *cis* compound

TABLE 1. Pairs of diastereomerically pure aminocyclopropane derivatives from a Hofmann or Curtius degradation[a]



	R^1	R^2	R^3	R^4	R^5	Transformation of X	Yield (%) [method[b]]	Reference
(37)	Ph	H	H	H	H	$COCl \rightarrow NH_2$	83 [A][149]	48, 103, 149
(38)	H	H	Ph	H	H	$COOH \rightarrow NH_2$	77 [B][40], 34 [C][149]	40, 48, 149
(39)	OPh	H	H	H	H	$COOH \rightarrow NH_2$	66 [B][42]	31, 42
(40)	H	H	OPh	H	H	$COOH \rightarrow NH_2$	57 [B][42]	31, 32, 42
(41)		H	H	H	H	$COOH \rightarrow NH_2$	52 [C][93]	37, 38, 42, 93, 113
(42)	H	H		H	H	$COOH \rightarrow NH_2$	31 [C]	93
(43)	Ph	H	H	H	Me	$COCl \rightarrow NH_2$	65 [B][42]	42, 158
(44)	H	H	Ph	H	Me	$COCl \rightarrow NH_2$	62 [B]	42
(45)	Ph	H	H	H	Ph	$COOH \rightarrow NH_2$	45 [B][126]	126, 170
(46)	H	H	Ph	H	Ph	$COOH \rightarrow NH_2$	50 [B][126]	126, 170
(47)		H	H	H	H	$COOEt \rightarrow NH_2$	37 [D]	13, 14, 26
(48)	H	H		H	H	$COOEt \rightarrow NH_2$	53 [D][c]	13, 14, 26

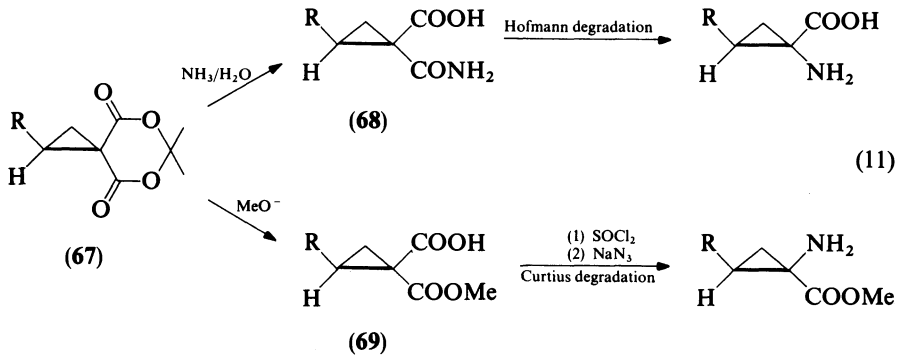
(49)	$-(CH_2)_3-$		H		H	H	COOH → $NHCONH_2$	80 [B][74]	17, 18, 58, 74
(50)	H	H	$-(CH_2)_3-$			H	COOH → $NHCONH_2$	73 [B][74]	17, 18, 58, 74
(51)	$-(CH_2)_4-$		H		H	H	COOH → NH_3^+	67 [B][110]	45, 46, 110
(52)	H	H	$-(CH_2)_4-$			H	COOH → NH_3^+	24 [B]	110
(53)	$-(CH_2)_5-$		H		H	H	COOH → $NHCONH_2$	75 [B]	74
(54)	H	H	$-(CH_2)_5-$			H	COOH → $NHCONH_2$	83 [B]	74
(55)	$-(CH_2)_6-$		H		H	H	COOH → $NHCONH_2$	53 [B][141]	16, 141
(56)	H	$-(CH_2)_6-$			H	H	COOH → $NHCONH_2$	54 [B]	88
(57)	X[d]	H	H		H	H	COOH → NH_3^+	65 [A][142]	49, 54, 55, 57, 64, 104, 142
(58)	H	X[d]	H		H	H	COOH → NH_3^+	32 [E][111], [55] A[112]	111, 132, 133
(59)	H	H	4-ClC_6H_4-		H	COOH	COOEt → NH_2	31 [C][118]	35, 48, 118
	H	H	4-ClC_6H_4-		H	COOMe	COOH → NH_2	41 [A]	35
(60)	4-ClC_6H_4-	H	H		H	COOEt	COOH → NH_2	53 [A][118]	35, 48, 118
	4-ClC_6H_4	H	H		H	COOH	$CONH_2$ → NH_2	45 [F]	35
(61)	H	H	Et		H	COOH	COOR → NH_2	41 [C]	151
(62)	Et	H	H		H	COOMe	COOH → NH_2	47 [B][151]	34, 151

[a] Further examples are reported in Refs 25, 43, 70, 75, 97, 113, 122, 139, 147.

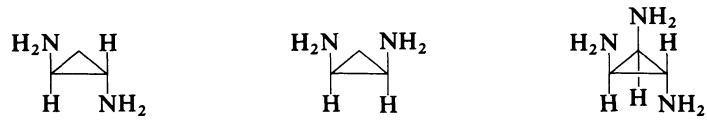
[b] A: RCOOH → RCOCl → $RCON_3$ → RNCO. B: RCOOH → RCOOCOOEt → $RCON_3$ → RNCO. C: RCOOEt → $RCONHNH_2$ → $RCON_3$ → RNCO. D: RCOOEt → $RCONH_2$ → RNH_2 (Hofmann degradation with Cl_2/NaOH). E: Method A and RNCO → RNHCOOBz → RNH_3^+ (hydrogenolysis). F: $RCONH_2$ → RNHCOOMe → RNH_2 (Hofmann degradation with Br_2, MeOH, MeONa).

[c] Not completely pure.

[d] Degradation of both functional groups X.

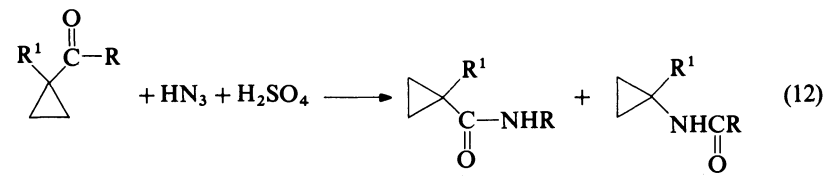


71 was reported to be difficult to obtain[49, 54, 55, 57]. Meanwhile, efficient syntheses are known starting from the bisazide[111, 132]. *Trans*-triaminocyclopropane (72) was also

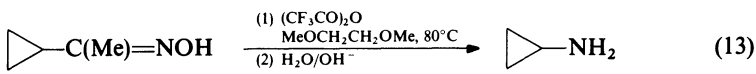


synthesized by Curtius degradation of the corresponding acid derivative[36, 49]; the Hofmann or Lossen reaction seemed not to be effective in this case[36]. Benzoylation of the less stable trihydrochloride of 72 led to a stable triamide[36]. Attempts to prepare a Schiff base from 72 caused an immediate ring-opening reaction[49].

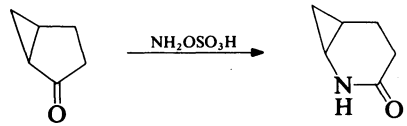
Cyclopropylamines were also obtained from cyclopropanecarboxylic acids (73, R = OH), hydrazoic acid and sulfuric acid in a Schmidt reaction[81, 178–180]. Cyclopropyl ketones (73, R = alkyl, aryl) as starting materials in the Schmidt reaction gave rise to a mixture of two isomeric amides (74 and 75) (equation 12). From ketones with an



unsubstituted cyclopropyl group (73, R^1 = H), 74 was formed in large excess over 75; only for R^1 = Ph was a predominant amount of 75 observed[181]. On the other hand, cyclopropane migration mainly took place when the concentration of H_2SO_4 was increased[182]. A Schmidt reaction at a cyclosteroid is known, too[182a].

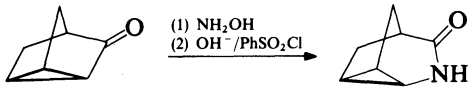


The Beckmann rearrangement also allowed the preparation of cyclopropylamines[16, 183–189]. **77** was accessible in 68–77% yield from the reaction of the oxime (**76**) with tosyl chloride in dioxane[183, 184] or with trifluoroacetic anhydride in dimethoxyethane[185] (equation 13). Bicyclic- and tricyclic aminocyclopropanes (**79** and **81**) could be obtained from ketones (**78** and **80**) and hydroxylaminic reagents[187, 188] (equations 14 and 15). Further examples are reported in Refs 188a–j.



(14)

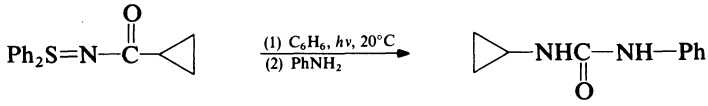
(78) **(79)**



(15)

(80) **(81)**

Finally, photolysis of the sulfilimine (**82**) afforded a cleavage similar to a Curtius degradation. The isocyanate intermediate was converted into the urea derivative (**83**)[190] (equation 16).



(16)

(82) **(83)**

13%

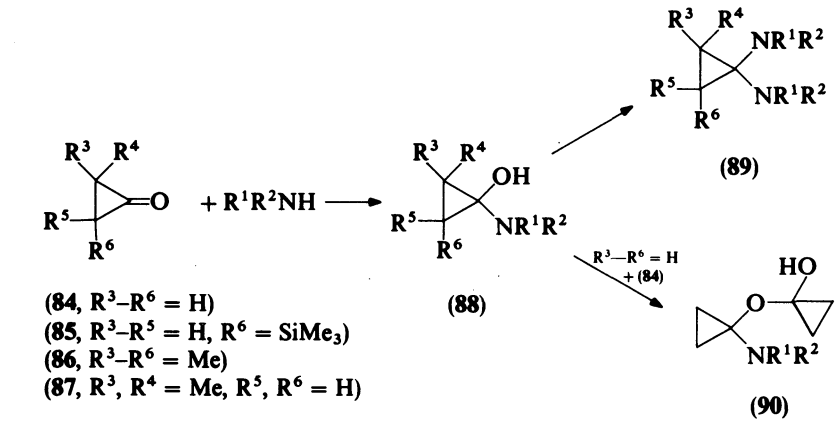
2. *Introduction by addition reactions*

a. Addition of amines to cyclopropanones

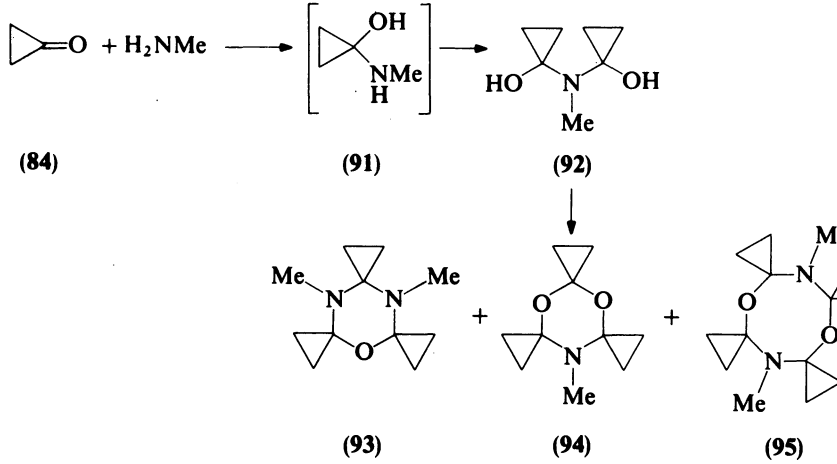
Amines add readily to cyclopropanones **84–87** forming O,N-semiacetals (**88**) as primary products[191–202]. These derivatives (**88**) could be used directly as starting materials for the synthesis of β-lactam compounds[194, 196, 197]. In some cases, however, subsequent reactions took place, which were strongly influenced by both the amino moiety in (**87**) and the reaction conditions.

With secondary amines, the O,N-semiacetal **88** normally could be isolated by application of special procedures[192, 195, 200, 201], e.g. addition of **84** to excess liquid dimethylamine at low temperatures gave **88** ($R^1 = R^2 = Me$) in 67% yield[192]. In some cases, subsequent substitution of the hydroxy group in **88**[191] or addition of more **84**[192] led to **89** and **90**, respectively (equation 17).

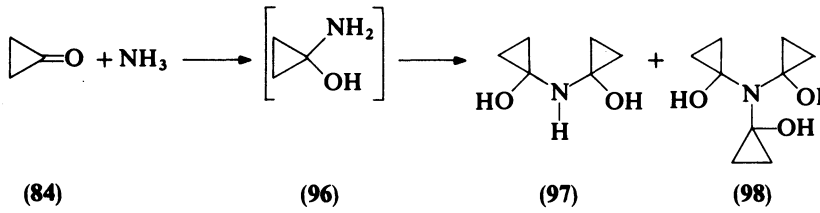
Addition products of type **88** could also be obtained from primary amines and **84** (at −78°C in ether[194] or dichloromethane[197]) or **86**[202]. Under other conditions subsequent reactions predominated in the addition of primary amines or ammonia to **84**. Thus, methylamine and **84** at low temperature yielded **92** as the main product but generated the



heterocycles **93–95** above 25°C[191, 193] (equation 18). The study of the kinetics gave an insight into the course of the generation of **93–95** and into the conditions for their selective preparation[193].

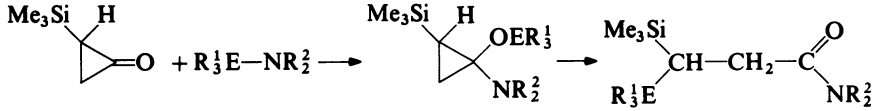


Similarly, the reaction of **84** with ammonia afforded **97** and **98** at −30°C (equation 19)[192]; changing the reaction conditions influenced the selectivity in favor of formation of either **97** or **98**. When, however, the reaction was carried out in liquid ammonia in the presence of NH_4Cl and addition of acid, **96** could be isolated after



separation from byproducts[203, 204]. The interaction of **84** with anilines was followed by ^{1}H-NMR spectroscopy[198, 199].

Stannyloxy-, germyloxy- or silyloxy compounds (**100**) were obtained from the addition of the organoelement amines (**99**) to the cyclopropanone **85** (equation 20). Because of a



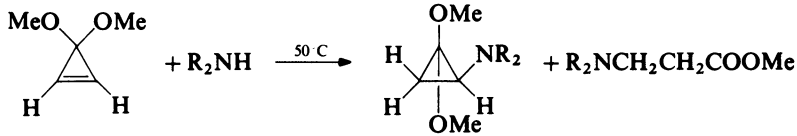
(**85**) (**99**) (**100**) (**101**)

E = Si, Ge, Sn (20)

very fast ring-opening of the stannyl or germyl derivatives (**100**), the addition reaction had to be run at −60°C and −30°C, respectively[205, 206].

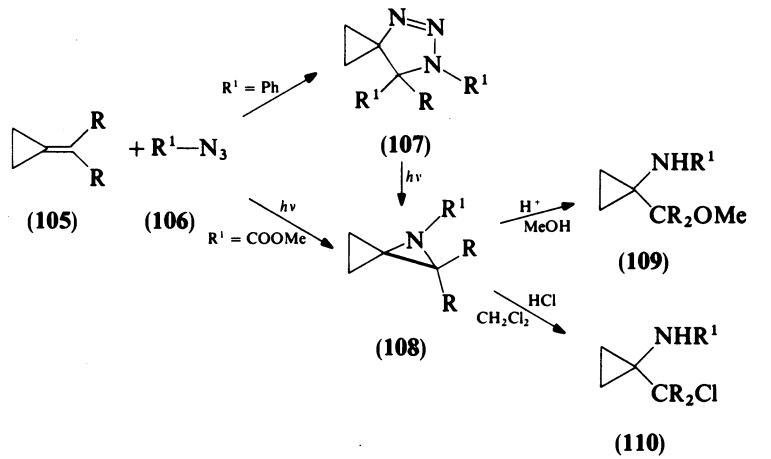
b. Addition of a nitrogen function to a cyclopropene or a methylenecyclopropane

Secondary amines reacted with cyclopropene (**102**) to give a mixture of **103** and **104**[207, 208] (equation 21). Diethylamine gave the cyclopropane **103** in 60% yield, diphenylamine generated **104** predominantly.



(**102**) R = Et, Pr, Ph (**103**) (**104**) (21)

Cycloaddition of phenyl azide (**106**, R^1 = Ph) with methylenecyclopropanes (**105**) followed by photolysis of the primary products (**107**) yielded spiro compounds (**108**), in which the aziridine ring could easily be cleaved by acids leading to **109** and **110**[209–212] (equation 22). Alternatively, compound **108** (R^1 = COOMe) was formed directly upon irradiation of methyl azidoformate (**106**) in the presence of excess **105**[211, 212].

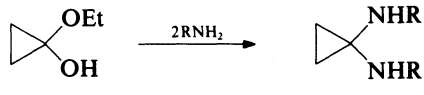


(**105**) (**106**) (**107**) (**108**) (**109**) (**110**) (22)

Reaction of a cyclopropene with diazomethane or an azide generated cyclopropanes containing an azo function[212–215]; a similar cycloaddition was reported for a nitrilimine[216]. Cycloaddition of an ethandiylidene biscyclopropane and triazolinedione led to a hydrazine derivative[217]. Reactions of these types forming azo- or hydrazinocyclopropanes are not subject of this review; however, they could be of interest for aminocyclopropane synthesis by functional group interconversion (for the cycloaddition of cyclopropyl azide with a carbon–carbon double bond see Section II.E.3, equation 101).

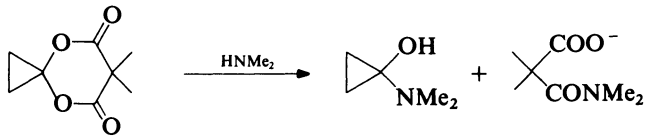
3. *Introduction by substitution reactions*

Nucleophilic displacements at a cyclopropane carbon atom without ring-opening generally require donor substituents at the three-membered ring or special bicyclic compounds (exceptions: dimethylaminocyclopropane formation in 19% yield from dimethylamine and *N*-cyclopropyl-*N*-nitrosourea[25]; introduction of an azido moiety by the reaction of cyclopropyl triflate with an azide[218]). The oxygen function in **111**, **113** and



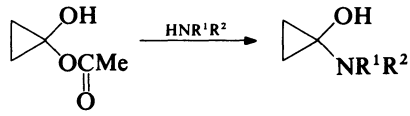
(23)

(111) **(112)**



(24)

(113) **(114)**



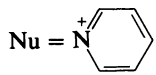
(25)

(115) **(116)**

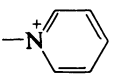
(26)

(117) **(118)**

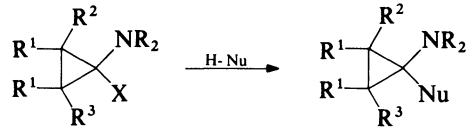
X = OH, Y = *p*-$MeOC_6H_4$

Nu = 

X = Cl, Y = *o*-HOC_6H_4

Nu = NMe_2, 

115 or a methoxy- or hydroxyphenyl group in **117** served as stabilizers for the cyclopropane ring in this way. Thus, aminocyclopropanes **112**, **114**, **116** and **118** could be obtained from amines and the starting materials **111**, **113**, **115** and **117**[197, 203, 204, 219–222] (equations 23–26). Analogously, an amino substituent in a cyclopropane (**119**), acting as a donor substituent, allowed the preparation of modified aminocyclopropanes (**120**) by nucleophilic substitution, e.g. displacement of OH or NR_2 in **119** by various nucleophiles (equation 27). The introduction of an amino function into **119** by such a method is discussed in Section II.E.



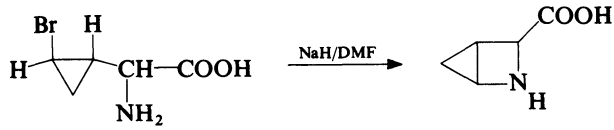
(27)

(**119**) (**120**)

$X = NR_2$, OH

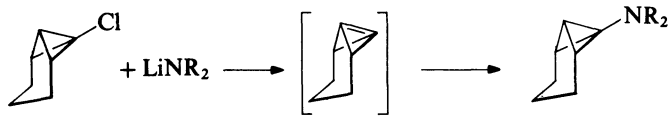
For examples for H-Nu, see Table 2

Strongly basic nucleophiles such as an amide ion allowed a nucleophilic substitution via an elimination–addition mechanism of cyclopropane derivatives possessing an acidic hydrogen atom[223a–d–225]. Aminocyclopropanes **121** and **122** were synthesized in this manner from the corresponding halogenocyclopropanes[223d–225] (equations 28 and 29).



(28)

(**121**)



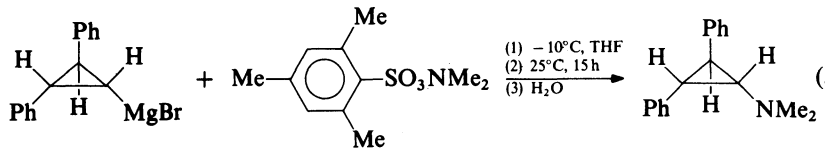
(29)

(**122**)

NR_2 = NMe_2, N 

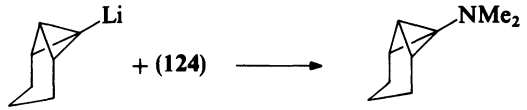
38–60%

Aminocyclopropanes have also been prepared from metalated cyclopropanes **123** and **126** by electrophilic substitution[226]. With **124** as amination reagent compounds **125** and **127** were obtained in fair yields (equations 30 and 31).



(30)

(**123**) (**124**) (**125**)



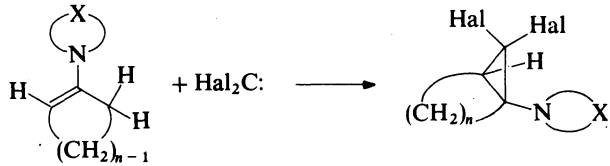
(126) (127) (31)

B. Cyclopropane Formation from a C(2) and a C(1) Unit

1. Cyclopropanation with carbenes or other methylene transfer reagents

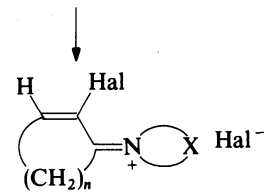
a. Simple enamines or β-acceptor-substituted enamines as C(2) units

(i) *Heterosubstituted carbenes as C(1) unit* In 1963 Ohno[227] reported the cycloaddition of dichlorocarbene onto enamines (**128**). Subsequently, the formation of aminocyclopropanes (**129**) from **128** and halocarbenes was investigated by several groups[228–250] (equation 32). $CHHal_3$ and *t*-BuOK[227, 228, 230, 233, 235, 242], $NaOCMe_2Et$[243], BuLi[235] or



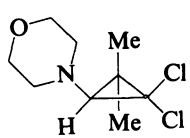
(128) (129)

	X
a	$-(CH_2)_4-$
b	$-(CH_2)_2O(CH_2)_2-$
c	$-(CH_2)_5-$

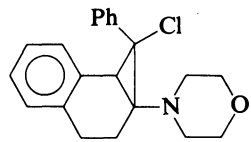


(130) (32)

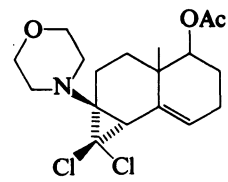
OH^-/phase transfer catalysis[235, 237, 240, 241, 245, 247, 249], $PhCHCl_2$/*t*-BuOK[232–234, 244], $CHClF_2/KOH$[250], $PhHgCBrCl_2$[235, 248], $PhHgCBr_3$[248], $PhHgCCl_2F$[235, 236] or CCl_3COO^- [229, 231, 233–236, 239, 241] have been used as halocarbene precursors. The yields of **129** depended strongly on the amino moiety and the ring size in **128** as well as on the mode of carbene generation. With morpholino- or piperidinoenamines (**128b, c**) the



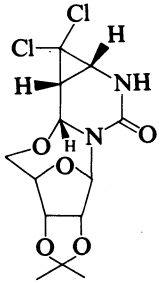
(131) 64% [237]



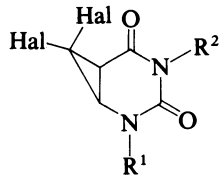
(132) 27% [233]



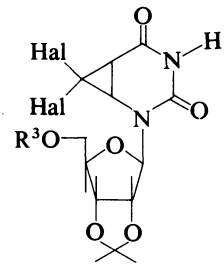
(133) 39% [235]



(134) 56%[248]



(135)[251]

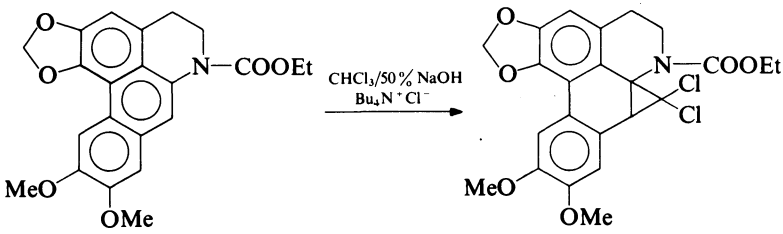


(136)[251]

Hal, Hal = Cl, Cl; Br, Br; Cl, F;
R^1, R^2 = Me, CH_2Ph; R^3 = Ac, CPh_3

cycloaddition products (**129**) generally could be isolated; especially phase transfer catalysis gave good yields. Besides the bicyclic systems (**129**), monocyclic or tricyclic derivatives have been synthesized, **131**, **132** and **133** being typical examples.

Less basic enamines (acylaminoalkenes[229] or vinylcarbazole[237, 238]) and a great variety of heterocyclic systems (parent compounds as well as oxo- or dihydro derivatives) were quite suitable starting materials, too (e.g. derivatives of indole[252a], carbazole[252b],



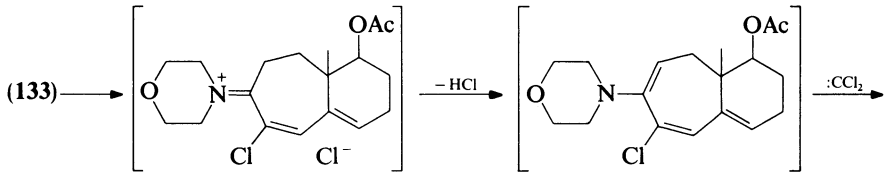
(33)

(137) (138)

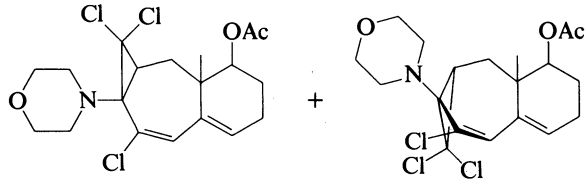
pyridine[252c], chinoline[252d, e], isochinoline[252f–k], benzoazepine[252l], azepine[252m–p], benzoazaphenalene[247], pyrimidine[251, 252k, q–s], the pyrrolizine anion[252t] or the pyridinium[253a–f] and the chinolinium[252f, 253g] cation). Thus aminocyclopropyl compounds **135**[251], **136**[251] and **138**[247] as typical examples were obtained from the corresponding precursors.

In contrast, pyrrolidinocycloalkenes (**128a**) in most cases gave iminium salts (**130**) which resulted from a ring-opening reaction of primarily formed aminocyclopropanes (**129**) (exceptions: reaction under phase transfer catalysis or steric hindrance of the ring-opening). Higher reaction temperatures or the presence of an acceptor group in the β-position of the enamine also caused the ring-opening of the morpholino derivatives, e.g. **133** and **144** (equations 34[235] and 35[241]); an excess of carbene additionally produced the aminocyclopropanes **141**, **142** and **146**, respectively, in low yields.

Thio-substituted carbenes which are generated from a chloromethyl sulfide and *t*-BuOK reacted with enamines **147** to give aminocyclopropanes **148** and **149**[254–256] (equation 36). In some cases, both isomers could be separated by chromatography (examples are given in equation 36)[254–256].

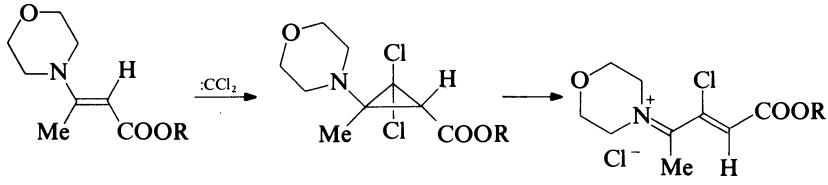


(139) (140)



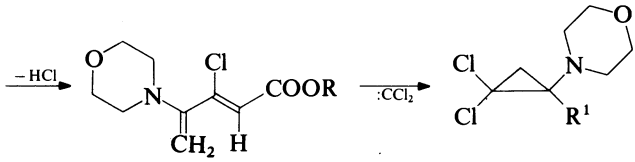
(34)

(141) (142)



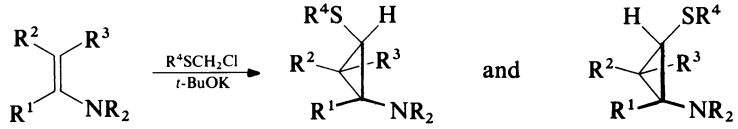
(143) (144)

(35)



(145) (146)

$R^1 = -CCl=CHCOOR$ and $-C\equiv C-$

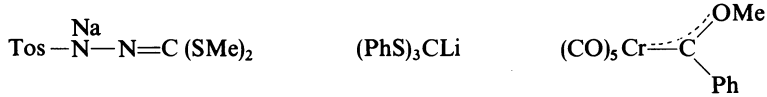


and (36)

(147) (148) (149)

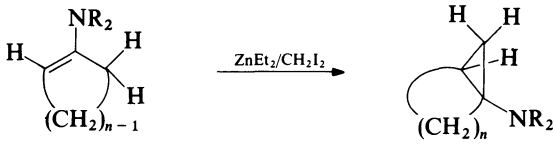
R^1 = H, R = R^2 = R^3 = Me, R^4 = *p*-ClC_6H_4	14%	isolated pure isomers	48%
R^1 = H, R = R^2 = R^3 = Me, R^4 = Me	2%	isolated pure isomers	13%
R^1 = R^3 = H, R = Me, R^2 = Ph, R^4 = *p*-ClC_6H_4	16%	isolated pure isomers	25%

Cycloaddition of a dithiocarbene onto enamines were performed starting with the carbene precursor **150**[257, 258] and **151**[259]. Cycloadditions of the carbene complex **152** with enamines are of no preparative interest because of very low yields and side reactions[260, 261] with lack of cyclopropanation in some cases[262, 263]. The intermediacy of carbenes in the coupling of dihalides with $W(CO)_6$ or $WCl_6/LiAlH_4$ were proved by trapping with enamines (giving the aminocyclopropanes in 1% and 13% yield, respectively)[264].

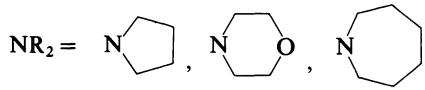


(150) **(151)** **(152)**

(ii) Simmons–Smith reagent as C(1) unit Many examples of aminocyclopropane formation from an enamine (**153**) and the Simmons–Smith reagent IZnCHRI (R = H, Me) have been reported[204, 241, 265–269] (equation 37). Simple enamines, aminodienes (cyclopropanation at the 1,2-double bond[269, 270]), acylaminoalkenes[271] or 1,1-diaminoalkenes[204]



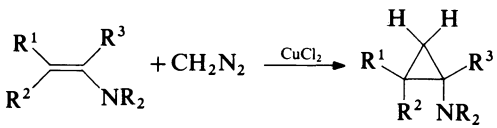
(153) **(154)** 32–71% (37)



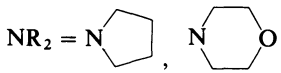
$n = 3, 4$

reacted in this way, preferentially with $ZnEt_2/CH_2I_2$. This reagent was found to be more satisfactory for large-scale preparations of aminocyclopropanes than diazomethane (see Section II.B.1.a.iii)[270]. With this method, no acceptor group is introduced into the molecule, therefore even when NR_2 was a strongly electron-donating residue (e.g. pyrrolidine or hexahydroazepine), no homoenamine reactions were observed[270]. From enamines containing an ester function in the 2-position ring-opened products were synthesized as a consequence of an homoenamine reaction of the primarily formed aminocyclopropanecarboxylic acid ester[241].

(iii) Diazoalkanes as carbene precursors Enamines (**155**) readily reacted with diazoalkanes in the presence of cuprous chloride or bis(acetylacetonato)copper(II) to give the



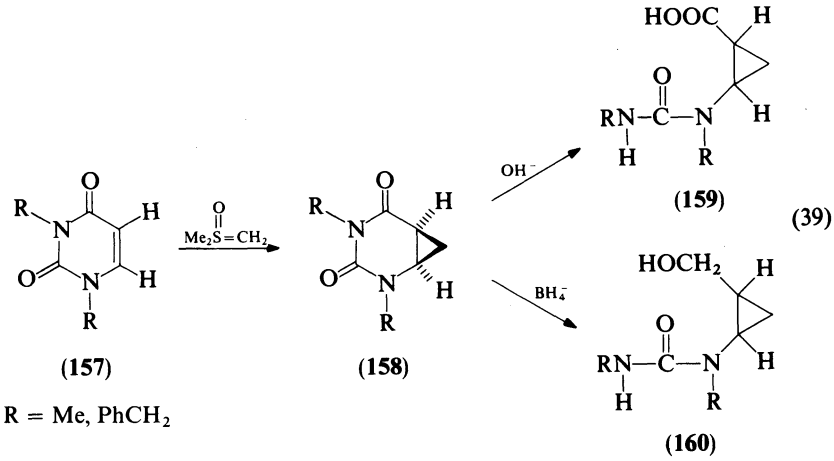
(155) **(156)** (38)



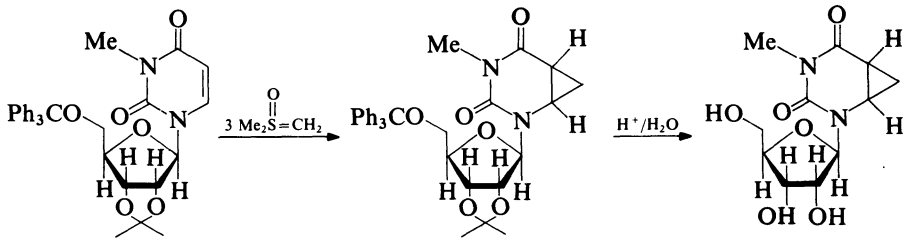
corresponding aminocyclopropanes (**156**)[67, 228, 270, 272–277] (equation 38). The reactivity of **155** decreased in the absence of alkyl groups; *N*-vinylamines required an excess of diazoalkane for cyclopropanation[272].

1,2-Diaminocyclopropanes could also be obtained from the corresponding 1,2-diaminoalkenes[278, 279]. For the formation of a cyclopropane from a 2-aryl substituted enamine, $Pd(OAc)_2$ was the catalyst of choice[280]. A great variety of *N*-heterocycles including pyrroles[281a–c], indoles[281d–g], di[281h]- and tetrahydro[281i] -pyridines, isochinolones[281j], pyrrolinedione[281k], pyrrolo[281l] and imidazolo[281m, n] -pyrimidines, uracils (**157**)[251], uridines (**161**)[251] and thiadiazinone dioxides[281o] have been cyclopropanated by diazomethane or alkyldiazoacetate.

(*iv*) *Dimethylsulfoxonium methylide as methylene transfer reagent* *N,N'*-Dialkyluracils (**157**) or *N*-alkyluridins (**161**) have also been converted to cyclothymins (**158**) and cyclothymidins **162** or **163** by dimethylsulfoxonium methylide[282] (equations 39 and 40).



(**157**) (**158**) (**159**) (**160**) (39)



(**161**) (**162**) (**163**)

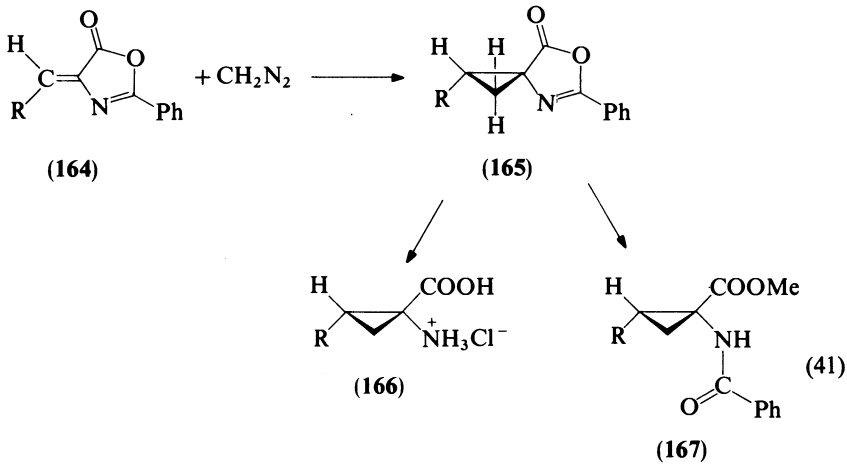
5.6H α 2.4% isolated
5.6H β 31% isolated

5.6H α and
5.6H β (40)

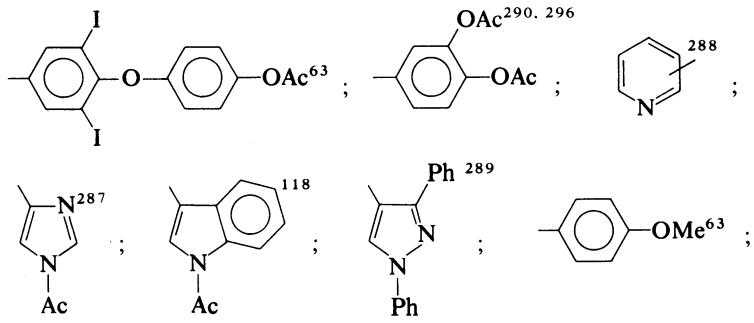
The cyclothymidin isomers (**162**) could be separated by chromatography. Interaction of **158** with hydroxide or sodium borohydride led to the aminocyclopropanes **159** and **160**. An analogous cyclopropanation was performed with 4-pyrimidones[283], pyridinediones[283a] or oxopyridopyrimidines[284].

b. Methylene oxazolones, thiazolones and imidazolones as C(2) units

Transfer of a methylene moiety from diazomethane to methylene oxazolones (**164**) was shown to be a useful approach to cyclopropane amino acids (**166**)[63, 118, 285–299]. Typical 'cyclopropylogs' of amino acids obtained by this method are given in equation 41.



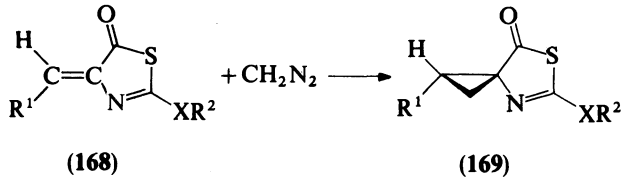
R = Ph[285, 291, 292] (pure *E*-isomer is also available[291, 292]);



—Cl[297] and —Me[292] (pure *E*-isomers are also available[292, 297])

Whereas the reaction **164** → **165** proceeded very easily, cleavage of **165** to **166** required special conditions. Acidic hydrolysis (HCl/AcOH) of the ester carboxamide (**167**)[291, 292, 297, 299] or a NHBOC derivative[291] or hydrogenolysis of the benzyl ester of **166**[291] proved to be most effective. Sometimes, however, the cleavage of **165** was not accomplished by these reactions[118, 290, 296, 300]. Amino acids (**166**) with R = aryl are normally obtained as *Z*-isomers after purification as a consequence of the *Z*-structure of the starting oxazolones; but *E*-isomers could also be synthesized from the corresponding *E*-oxazolones[291, 292, 298, 299]. A study of the steric course of the cyclopropanation with *Z*- and *E*-isomers of **164** (R = aryl) in detail showed a fair stereoselectivity. When the methylene oxazolone contained only one or no aryl group at all, less[298] or lacking[292, 299] stereoselectivity in the cyclopropane formation was observed.

Methylene thiazolones (**168**)[286, 301–304] or methylene imidazolones (**171**,



(168) **(169)**

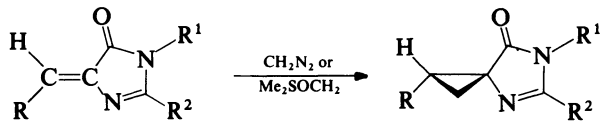
X = O, S

(1) EtOH/KOH, 20°C
(2) H^+

(42)

R^1 = Ph (pure *E*-isomer is also available[304]);

(170)

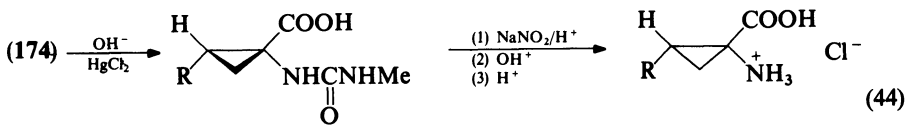


(43)

(171) $R^1 = R^2$ = Ph **(173)**

(172) R^1 = Me, R^2 = SMe **(174)**

172)[286, 305, 306] and diazomethane reacted in a similar way (equations 42 and 43). The unproblematic hydrolysis of the spiro compounds **169** and **174** coupled with their stereoselective formation favors these sequences. Spiro compounds (**169**, X = S) are hydrolyzed by ethanolic sodium hydroxide; for the analogous hydrolysis of the alkoxy compounds (**169**, X = O) heating is necessary[301, 303]. Spiroimidazolones (**172**) were transferred into aminocyclopropanes (**166**) by $HgCl_2$ treatment and cleavage of the ureido derivative (**175**) by diazotation[306] (equation 44).

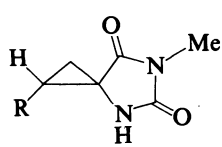


(44)

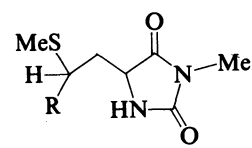
(175)
and side products

(166)
R = Ph, *p*-$MeOC_6H_4$, $-CHMe_2$
(also pure *E*-isomers are available)

side products:

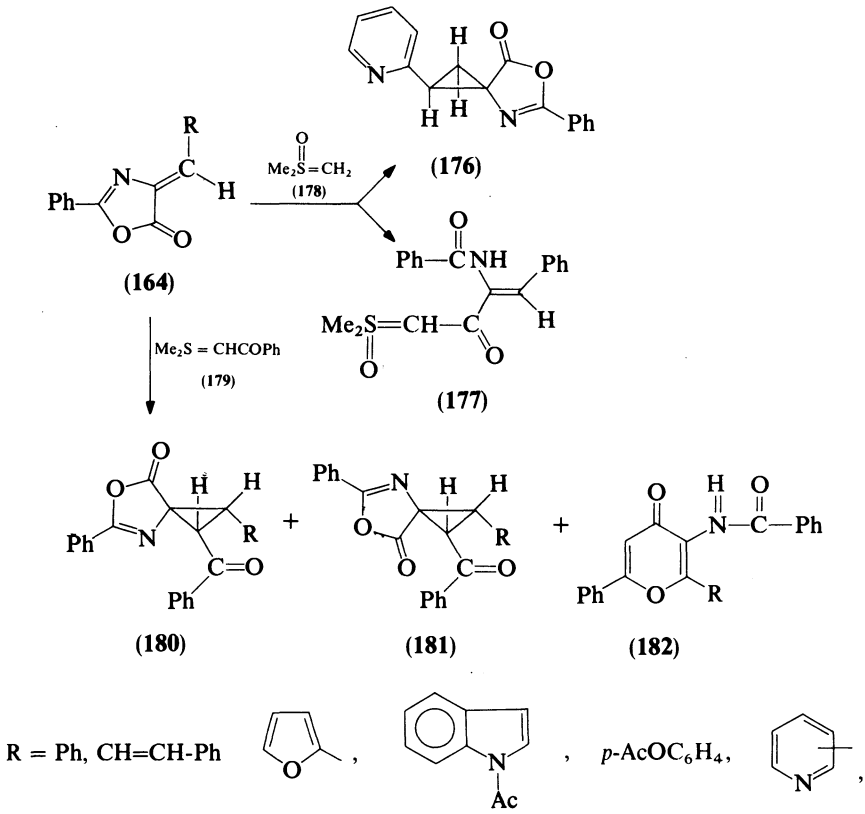


and



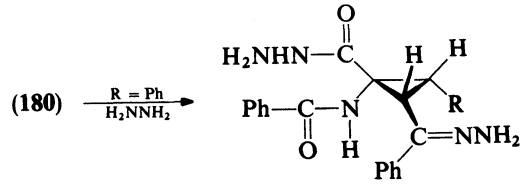
Methylene insertion reactions into the olefinic CH bond of **164**, **168** and **171/172** by diazomethane have been reported several times[286, 292–294, 298, 305]. In most of these cases the percentage of cycloaddition product could be increased by appropriate reaction conditions[293, 294, 298, 305].

Sulfurylides as methylene transfer reagents were not suitable in every case. Sulfoxonium ylide (**178**) and the pyridyl derivative (**164**, R = pyridyl) formed the cyclopropane (**176**)[288], but the same reagent generated an acylated sulfoxonium ylide (**177**) with a phenyl compound (**164**, R = phenyl)[307] (Scheme 2). The less reactive sulfonium ylide (**179**) and

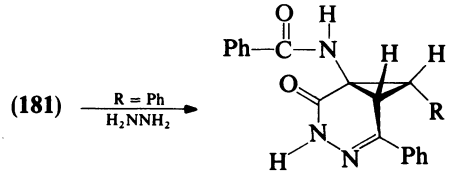


SCHEME 2

methylene oxazolones (**164**) gave a mixture of two isomers (**180** and **181**) besides small amounts of the side product (**182**)[302]. The yields of **180** and **181** were influenced by reaction time and reaction temperature. The configuration of chromatographically separated diastereomers (**180** and **181**) was established after hydrazinolysis. Contrary to **180** (equation 45), the *cis*-diacyl arrangement in **181** gave rise to a bicyclic aminocyclopropane derivative (**184**)[307] (equation 46).



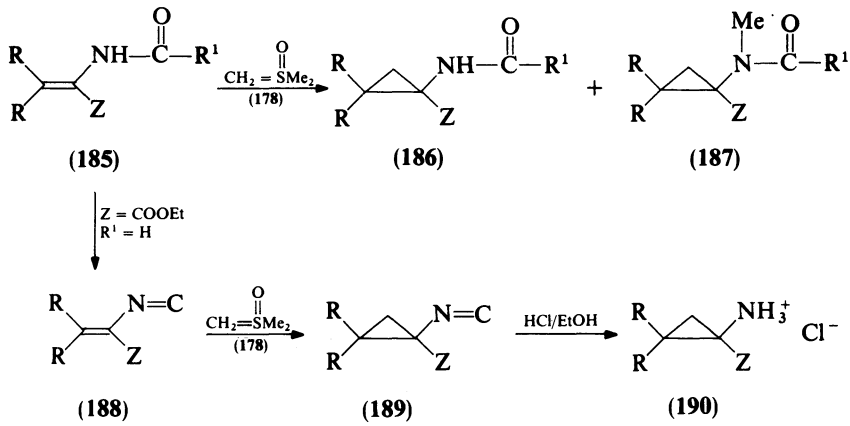
(183) (45)



(184) (46)

c. Electron-deficient double bonds with a nitrogen function as C(2) units

An electron-deficient double bond bearing an isonitrile group was used for aminocyclopropane preparation by a [2 + 1] cycloaddition[308,309] (Scheme 3). Reaction of **188** with



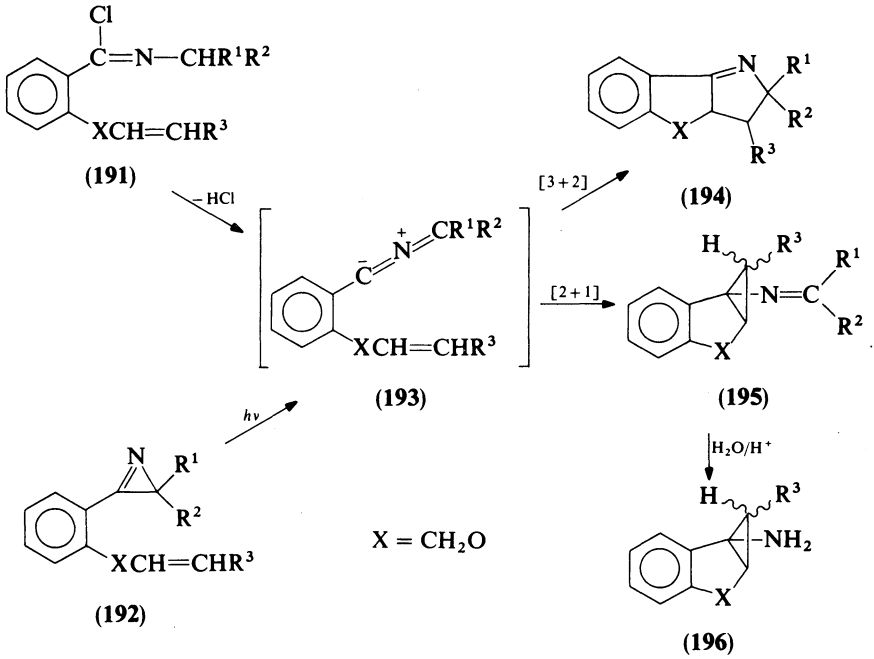
Z = COOEt, Ts R = H, Me, Et; R, R = $-(CH_2)_5-$

SCHEME 3

the sulfoxonium ylide (**178**) and subsequent hydrolysis yielded the aminocyclopropanes (**190**). Thereby, the use of the isocyano derivative (**188**) was superior to direct cyclopropanation of the *N*-formyl derivative (**185**). Lower reactivity, poorer yields and formation of mixtures of **186** and **187** are disadvantages of the latter process[308]. An isocyano cinnamic ester (1:2.6 *E*/*Z* mixture) generated the *Z*-isocyano cyclopropane with high stereoselectivity (40:1 ratio)[308].

d. Normal carbon–carbon double bonds as C(2) units

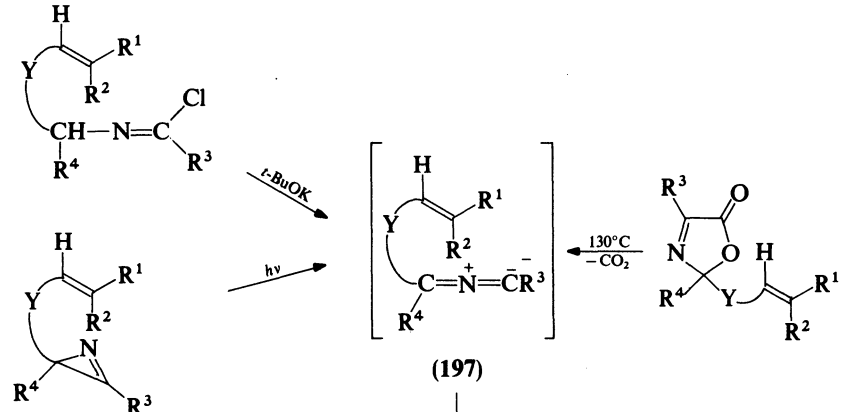
Formation of aminocyclopropanes in a carbene cycloaddition to a carbon–carbon double bond containing no nitrogen function requires an amino-substituted carbene as counterpart. Such a type of reaction was observed with special nitrile ylides possessing a suitable double bond within the molecule[310–314]. Thus, nitrile ylides (**193**) generated from the precursors **191** or **192**, underwent intramolecular [2 + 1] or [2 + 3]cycloaddition yielding **194** and **195** respectively (Scheme 4). **195** was easily hydrolyzed to aminocyclopropane (**196**). The preferential direction of the cycloaddition was influenced by the nature



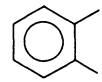
SCHEME 4

of the substituents R^1, R^2 and R^3. Exclusive cyclopropane formation was reported for **193** ($R^1 = R^2$ = Me and R^3 = H, Me or $R^1 = R^3$ = H and $R^2 = CH_2C_6H_4NO_2$). On the other hand, **193** with $R^1 = R^2$ = H or R^3 = COOMe furnished only **194**. It was suggested, that the geometry of the 1,3-dipole determines the course of the cycloaddition. A bent 1,3-dipole should favor formation of **195**[312,313]. In intermolecular cycloadditions of nitrile ylides with carbon–carbon double bonds a [2 + 1] reaction did not occur[126].

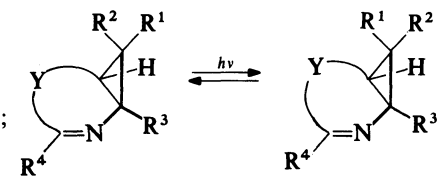
Cyclopropanes (**198**) were obtained in good yields from an intramolecular [1 + 2] cycloaddition of nitrile ylides (**197**) generated from chloroimidates and *t*-BuOK[312,314] or thermolysis of oxazolinones[313] (equation 47). The cycloaddition was shown to proceed stereospecifically[313,314]. Bicycles (**198**) isomerized to compounds **199** upon irradiation[313]. Therefore the product spectrum derived from nitrile ylide cycloaddition became more complex when nitrile ylides (**197**) were formed by a photoreaction of the corresponding azirines[312]. The lack of stereospecificity initially was discussed in terms of a two-step reaction.

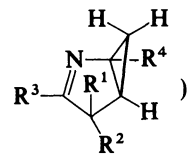


(47)

Y =  ; $-CH_2-$

R^1, R^2 = Me/CD_3; H/Ph; Me/H; H/H; H/COOMe



(Y = CH_2: also isomerization to )

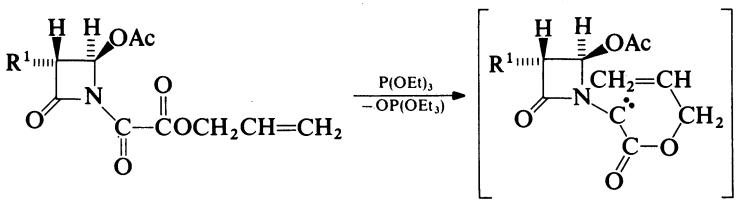
The formation of **202** and **203** from **200** and $P(OEt)_3$ was interpreted as a cycloaddition of the carbene intermediate **201** (equation 48); the two isomers **202** and **203** were isolated in 30% and 12% yield, respectively[315].

Photolysis or thermolysis of the tungsten carbene complex (**204**) generated the aminocyclopropane (**205**) (equation 49). Triphenylphosphine proved to be an efficient catalyst for the decomposition of **204**[316].

2. *Cyclopropanation with dianion precursors*

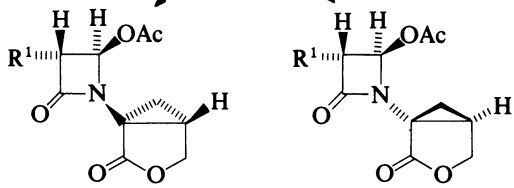
a. Dianion precursors and a C(2) unit

An isocyano moiety in **206a**[203, 308, 317–322] or a Schiff base in **206b**[323–326] were used as masked amino function for the synthesis of aminocyclopropanes according to equation 50. Methyl isocyanides with a carboxylic ester, a phosphonic ester or a tosyl function (TosMIC) (**206a**) proved to be suitable starting materials. 1,2-Dibromoethane was superior to ethane derivatives with another halogen- or a tosyl leaving group as the C(2) unit[308,317]; secondary or tertiary dihalides failed to give cyclopropanes in this way[308,317]. Tetradeuterated[322,324] and specifically dideuterated[320,322,326] aminocyclopropane carboxylic acid derivatives were prepared from **206a** or **206b** and the corresponding

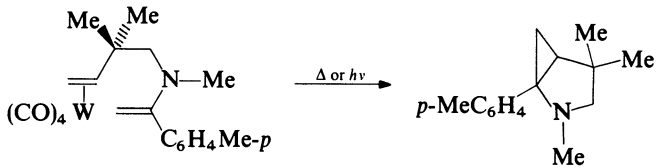


(200) (201)

(48)

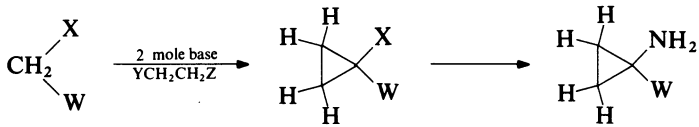


(202) (203)



(204) (205)

(49)



(206) (207) (208)

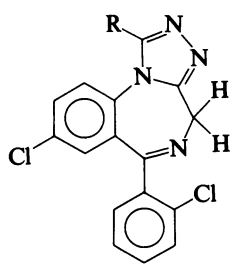
(50)

(206)

a X = $-N\equiv C$, W = COOEt, $PO(OR)_2$, Tos

b X = $-N=CHAr$, W = COOEt, $PO(OR)_2$

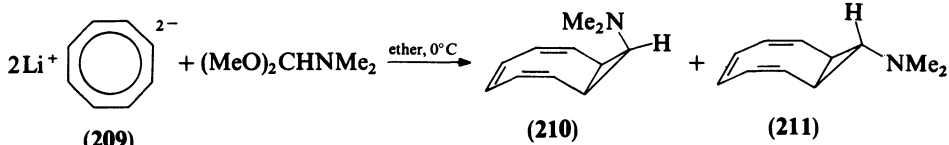
(206c)



deuterated dibromoethanes. Hydrolysis of the isocyano group or of the imine moiety in **207** led to the aminocyclopropanes **208**. The methylene group in **206c** was also acidic enough for cyclopropanation with bromochloroethane[327].

b. Dianion precursor and a C(1) unit

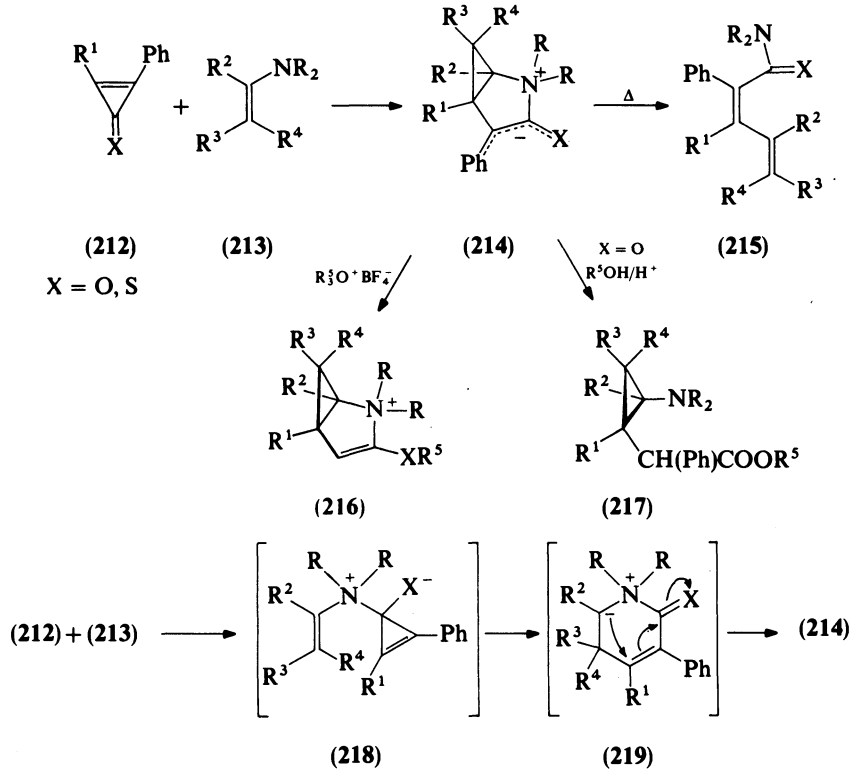
Cyclopropanation of **209** by a formamide acetal represents a cyclopropane synthesis from a dianion and a C(1)unit[328]. **210** and **211** were formed in a 6:4 ratio (equation 51). No rearrangement of **210** and **211** could be detected on standing at 70°C in C_6D_6.



(209) **(210)** **(211)** (51)

3. Cyclopropanation with cyclopropenones and -thiones as C(1) unit

Contradictory interpretations and results were reported initially for the reaction of enamines (**213**) with cyclopropenones or -thiones (**212**) (for reviews, see Refs 329, 330). Later it was shown that the cyclopropyl ammonium derivatives (**214**) were obtained as



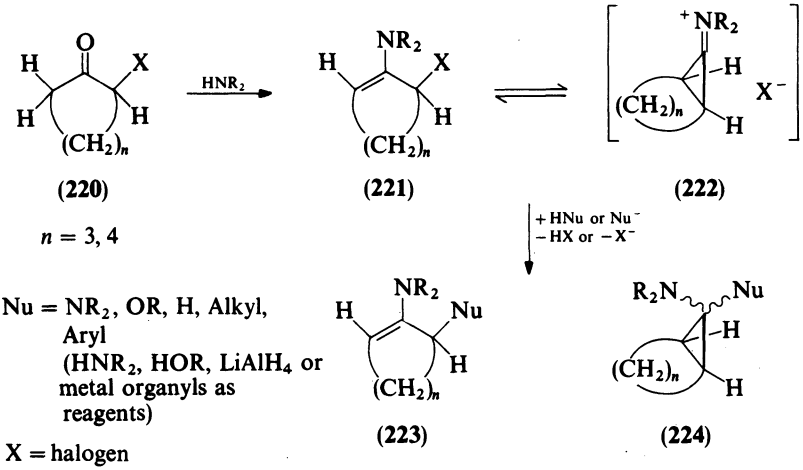
SCHEME 5

primary products from **212** and **213** at ambient temperature[331–334] (Scheme 5). At higher temperatures **214** decomposed into **215**; consequently, compounds **215** were also the main products from the reaction of **212** and **213** at 80°C (see also Refs 335–338). **218** and **219** were assumed to be intermediates in the formation of **214**. The products **214** sometimes proved to be isomerically pure, in other cases *exo/endo* isomers resulted. Phenylmethylcyclopropenone or phenylcyclopropenone were added regiospecifically. The latter reacted with some enamines (**213**) in a 2:1 stoichiometry[333]. Ketene-*N*,*Z*-acetals (*Z* = OR, SR, NR_2) also could be converted into ammonium cyclopropanes (**214**) by reacting with **212** at room temperature[339]. Some imines reacted with thiocyclopropene (**212**) in a similar way[339a, b]. Various reactions of **214** have been studied[331–334, 339, 340]; thus, further aminocyclopropane derivatives like **216** and **217** have been accessible.

C. Cyclopropane Formation by 1,3-Ring-closure

1. *Halogeno enamines as starting materials*

Szmuszkovicz and coworkers[17, 18, 58, 341–343] obtained bicyclic aminals **224** in addition to **223** from the interaction of secondary amines with seven- or six-membered cyclic chloroketones (**220**) (equation 52). The yields of **224** were influenced by the nature of the



(**220**) (**221**) (**222**)

n = 3, 4

(52)

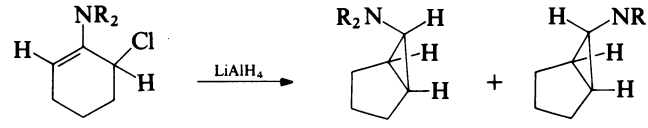
Nu = NR_2, OR, H, Alkyl, Aryl (HNR_2, HOR, $LiAlH_4$ or metal organyls as reagents)

X = halogen

(**223**) (**224**)

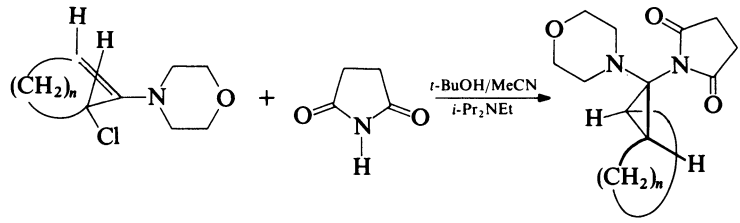
halogen in **220**[334]. Chloroenamines (**221**) which are the primary products in these reactions were also used as starting materials[344–349]; mechanistic pathways, e.g. participation of **222**, have been discussed[347]. Sometimes a strong selectivity for cyclopropane formation was observed with special reagents: excess dimethylamine in the presence of $AgBF_4$ produced **224** almost quantitatively[345]; the same reaction with a non-cyclic chloroenamine required somewhat different conditions[346]. Among metal organyls as nucleophiles, magnesium organyls seemed to be better suited for the synthesis of **224** than lithium organyls or lithium cuprate complexes; the latter exclusively generated **223** from **221**[347]. Complex hydrides yielded a mixture of *exo*-amine (**227**) and *endo*-amine (**226**) from the chloroenamine (**225**) (equation 53)[347, 348]. **226**, being the main product, and **227** could be separated by extraction with buffer solutions[348].

On treatment of **221** with alkoxides having a bulky alkyl moiety, **224** was formed in addition to **223** (Nu = OR')[344]. It was shown that 10–12-membered cyclic chloroenamines (**228**) and succinimide (**229**) in the presence of a tertiary amine gave *trans*-bicyclic



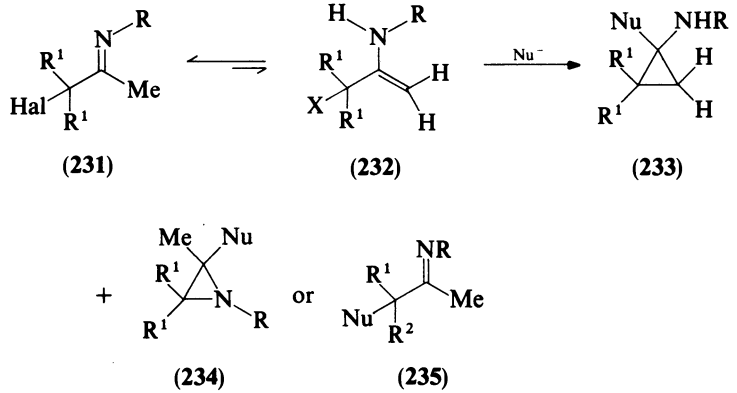
(225) (226) (227) (53)

compounds (**230**) with 95–98 % stereoselectivity[349] (equation 54). The mixture of **228** and **229** was obtained in a one pot procedure from *N*-chlorosuccinimide, dimethyl sulfide and an enamine (see Section II.C.2)[350,351].



(**228**, n = 7–9) (**229**) (**230**, n = 7–9) (54)

Aminocyclopropanes **233** were isolated besides other products in the reaction of α-halogenoalkyl imines (**231**) with some nucleophiles, e.g. CN^- or $R'O^-$ [352–354] (equation 55). **233** stems from an attack of the nucleophile on **232** which is the tautomer of

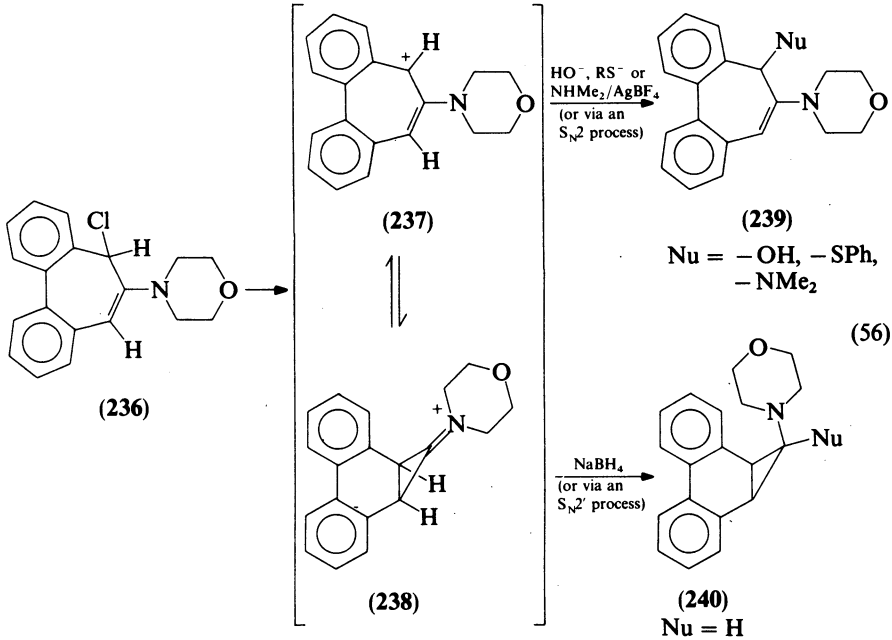


(**231**) (**232**) (**233**) (55)

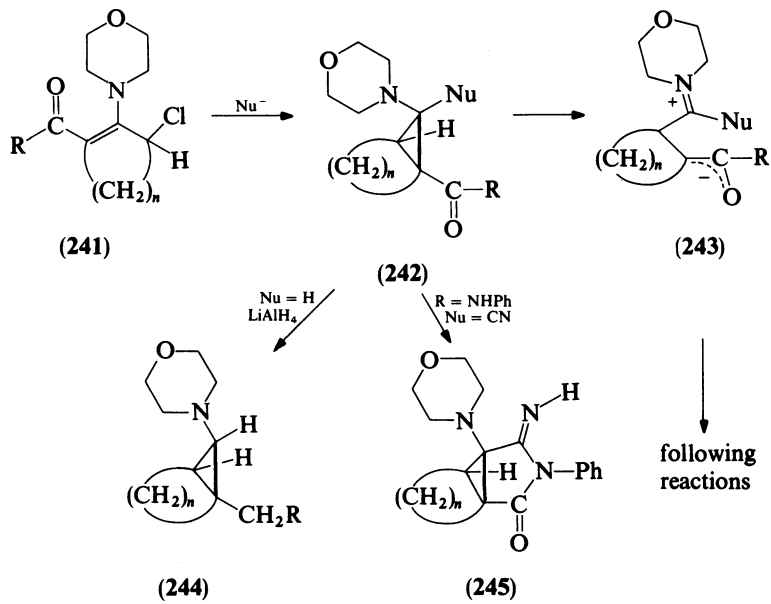
(**234**) (**235**)

231. For the formation of **233**, a tertiary alkyl halide was necessary (R^1 = Me); a bulky group R at the imino moiety increased the yield of **233** (see also Section II.E.2, equation 98).

The preparation of aminocyclopropane derivatives from substituted chloroenamines showed some restrictions. The substituent influences both the energy difference between aminoallyl cation and cyclopropaniminium ion and a subsequent homoenamine ring-opening. Thus, the stabilization of the positive charge in a dibenzotropylium species (**237**) may be the reason for the formation of **239** from **236** and nucleophiles like OH^-, $HNMe_2/AgNO_3$ or RS^- [355]. So far, only treatment of **236** with sodium borohydride led to aminocyclopropane compound **240** (Nu = H)[355] (equation 56).

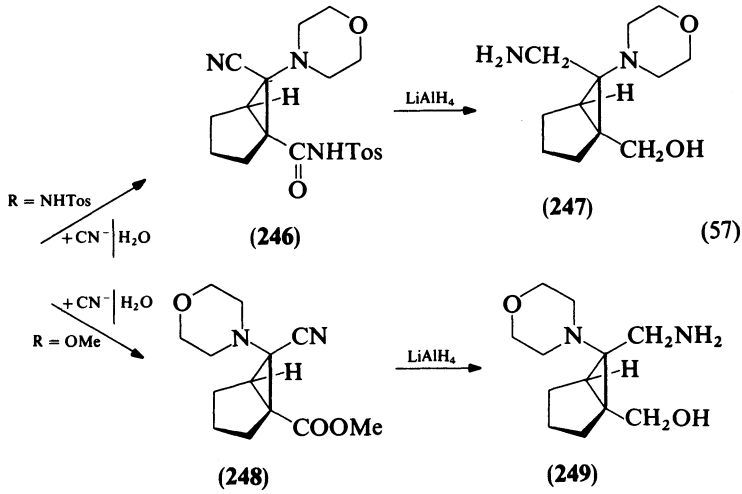


Aminocyclopropanes with an acceptor substituent in the β-position (**242**) could be prepared from the corresponding chloroenamines (**241**) preferentially with CN^- as



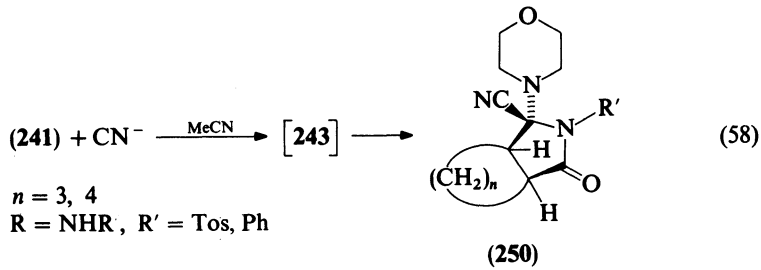
SCHEME 6

nucleophile in water as solvent[356] (Scheme 6). Thereby bicyclic *endo*-morpholino nitriles **242** (Nu = CN) and **248** were obtained from chloroenamines **241** with R = OR′ (n = 3) or NHTos (n = 5). Instead of the anilido derivative (**242**, n = 3) cyclization product **245** was isolated from a subsequent amine nitrile attack. Exclusive formation of *exo*-morpholino-bicyclo[3.1.0]hexyl carbonitrile (**246**) is an exception in this reaction scheme. $LiAlH_4$ reduction of **246** and **248** proved to be an easy and highly stereoselective access to diastereomeric compounds **247** and **249**[356] (equation 57).



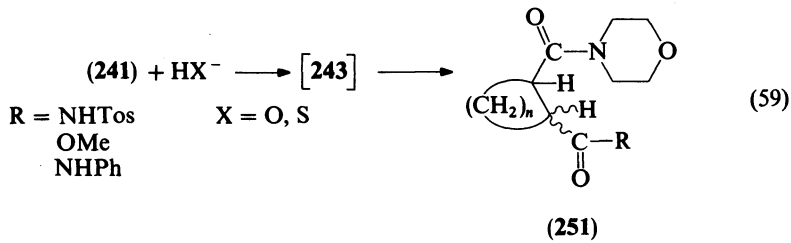
(57)

Surprisingly homoenamine products formally derived from **242** were obtained from **241** (R = NHPh or NHTos) and cyanide in acetonitrile as solvent (equation 58)[357].



(58)

A homoenamine reaction was also observed with OH^- or SH^- as nucleophiles causing a ring opening of **242** to a zwitterion (**243**), which by proton migration, gave **251**[357] (equation 59).

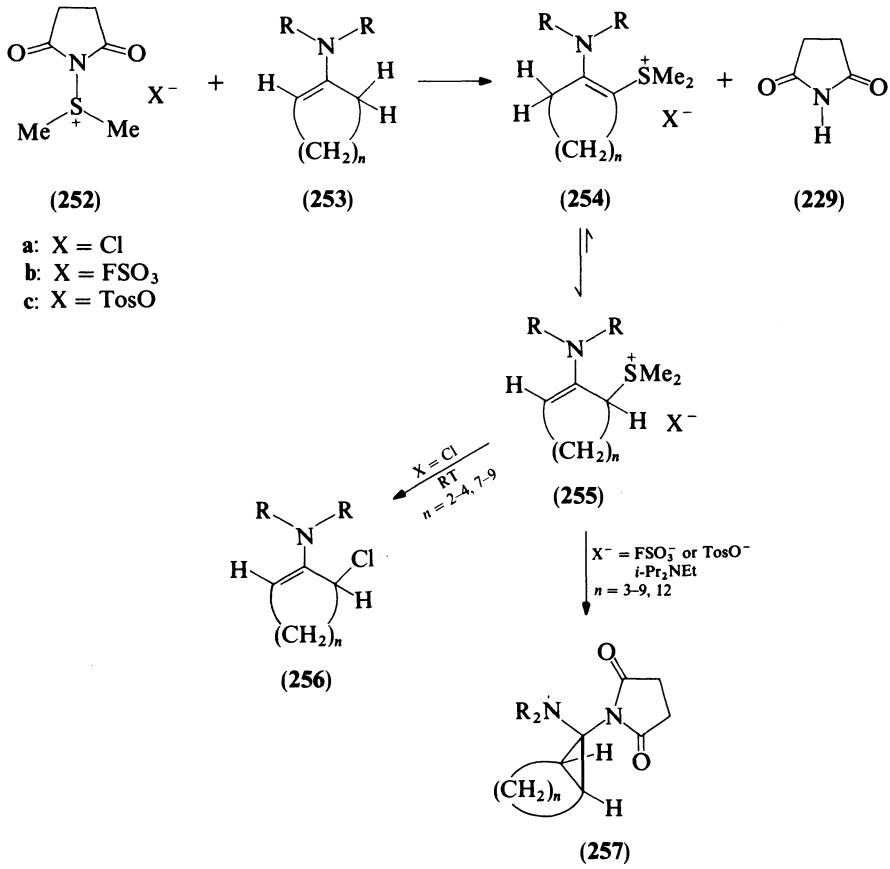


(59)

Hydride as a nucleophile converted **241** into the aminocyclopropanes **244** in fair yields[356]. Here, a ring-opening reaction was prevented by removal of the acceptor carbonyl group in **242** by reduction (Scheme 6). A [2.1.0]-bicyclic system was accessible by this sequence too.

2. Enamino sulfonium salts as starting materials

A widely applicable access to bicyclic aminocyclopropanes was outlined by Vilsmaier and coworkers[348–351,358–375] on the basis of enaminosulfonium salts. A sulfonium group could be easily transferred to an enamine (**253**) by the imidosulfonium salt (**252**). Thereby, the primarily formed vinylsulfonium salts (**254**) rearranged to the more stable allylsulfonium salts (**255**)[350,351]. The imidosulfonium chloride (**252a**) as starting material yielded enaminosulfonium chlorides (**254a/255a**), which decomposed at room temperature in solution within 1–3 days to chloroenamines (**256**) (Scheme 7). Exchange of the chloride anion in **252**, **254** or **255** by the fluorosulfate anion or in **254/255** by a tosylate, tetraphenylborate or a hexafluorophosphate anion led to stable sulfonium salts



SCHEME 7

(**254**/**255**)[375]. Addition of a tertiary amine to a mixture of **255b, c** and **229**, obtained from **252** and **253** after anion exchange, generated the aminocyclopropanes **257** in good yields[348,358,359,368,369]. The ring size in **255** could be varied from 6 to 15 carbon atoms. Under certain conditions, *cis* isomers (**257**) in the field of medium- and large-ring systems were obtained exclusively. In this special case enaminosulfonium chlorides (**255a**) could also be used, in the presence of *tert*-butanol[348] or by using low reaction temperatures[359].

After separation from **229** the enaminosulfonium salts **254b** or **255b** could also be treated with other nucleophiles to give a variety of aminocyclopropane derivatives[348,360–367,369–374] (Scheme 8). Thus, starting from **258** there were obtained **259** with alkoxide[360,369], **260** with thiolate[372], **261** with hydroxide[360,369], **262** with potassium cyanate[365], **263** with sodium azide[371] or **264** with sodium cyanide[362,369].

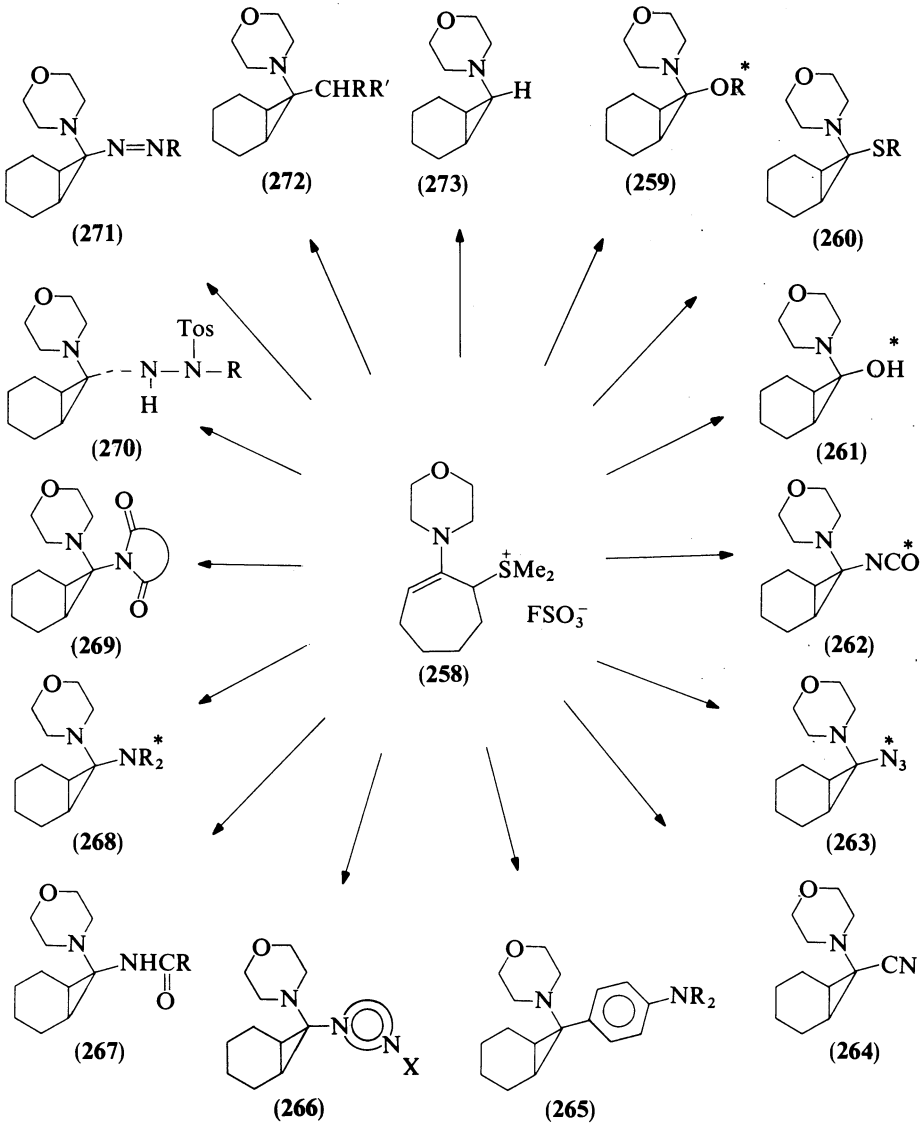
Interaction of **258** with anilines or five-membered nitrogen heterocycles produced **265** and **266** via an aminoalkylation[364,373,374]. Bicyclic derivatives **267–271** with an aminal structure resulted from the interaction of **258** with amides[365], urethanes[365], imides[363], ureas[365], amines[360,369] or hydrazines[367]. Finally, **272** was formed with carbon acids[366] and a reduction to **273** occurred with the sodium salt of formic acid[348]. It is not yet totally clear whether an iminium ion is involved in the formation of **259–273**. The yields of isolated products varied from 45 to 95%.

All primarily formed compounds were shown to be *endo*-morpholino isomers. Derivatives marked with an asterisk isomerized to the corresponding *exo*-isomers upon heating or in the presence of acids. Starting from **258** pure *endo*- and *exo*-morpholino compounds could be obtained in the case of **263**[371] and **266** (benzyltetrazole as the heterocycle)[373,374]; the diastereomers of **259** and **261** were synthesized more conveniently from **268**[360,369] (see Section II.E.1). Reaction of **258** with cyanate either led to a trimer of **262** (at ambient temperature) or to the *exo*-morpholino diastereomer of **262** (at higher temperature)[365].

The information on the *endo*- or *exo*-position of a nitrogen heterocycle in a [n.1.0]bicyclic system could be obtained in an easy way from ^{1}H-NMR spectroscopy: the two hydrogen atoms of the NCH_2 group of an achiral *N*-heterocycle are interconverted by a combination of three dynamic processes (ring inversion, nitrogen inversion and rotation about the exocyclic N–C bond). It was found, that these dynamic processes of a morpholino, piperidino, pyrrolidino or hexahydroazepino moiety are more or less strongly hindered in the *endo*-position, but are not affected in the *exo*-position. The frequency of interconversions of the two hydrogen atoms can be evaluated by a dynamic ^{1}H-NMR study.

In the most favorable case, e.g. bicyclohexane, -heptane- or -octane system, the *endo*/*exo*-assignment could be based upon the type of the ^{1}H-NMR signals of the nitrogen heterocycle: thus in the ^{1}H-NMR spectrum at room temperature an AA′XX′ pattern (more frequent interconversions) is observed for an *exo*-morpholino and an ABXY system (less frequent interconversions) for an *endo*-morpholino moiety. [n.1.0]Bicycles with $n \geqslant 8$ required the study of the dynamics of the nitrogen heterocycle by temperature-dependent ^{1}H-NMR spectroscopy; in these cases hexahydroazepine proved to be the best 'stereo-indicator'[359]. Further information on this method of assignment of configuration is given in Ref. 376 and in the original literature[348,349,358–375,377–382]. A qualitative differentiation of diastereomers based upon split off or not split off ^{1}H-NMR signals of a bridgehead bonded morpholine in a [n.1.0]bicyclic system was reported by Pandit and his group[233–235].

In some cases two steps proved to be necessary for aminocyclopropane synthesis from enaminosulfonium salts. Strongly basic nucleophiles, e.g. Grignard reagents[377], caused ylide formation from **258** followed by a 2,3-rearrangement. The cyclohexenylsulfonium salt (**254**, $n = 3$) was attacked by several nucleophiles at the sulfonium methyl group causing a demethylation reaction[370]. Finally, the strong *cis*-stereoselectivity observed with



* The isomers can be isomerized to the *exo* isomers.

SCHEME 8

succinimide **229** and **255** in the case of medium- and large-ring systems could not be maintained with other nucleophiles, e.g. CN^- [362].

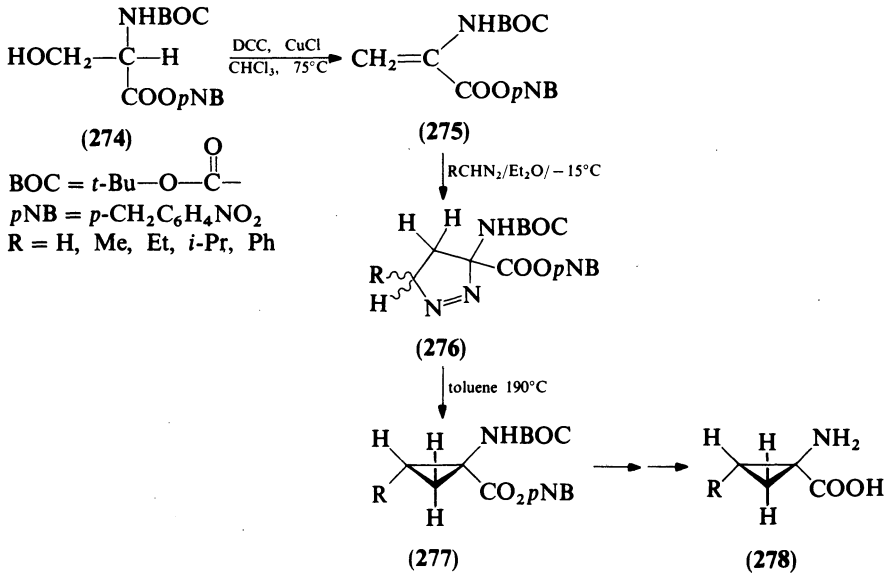
All these difficulties could be circumvented by synthesizing first the succinimido derivatives (**257**) and displacing in a second step the succinimido moiety in **257** by other

nucleophiles[348,359,370,377–382]. Analogously, *trans*-aminobicycloalkanes were best prepared by similar reactions with the *trans*-succinimido compounds (**230**)[348,378,379]. The latter were obtained also from enaminosulfonium salts via chloroenamines (**228**) (see equation 54 and Scheme 7; for examples see Section II.E.1, equations 93 and 94).

3. Ring-contraction reactions

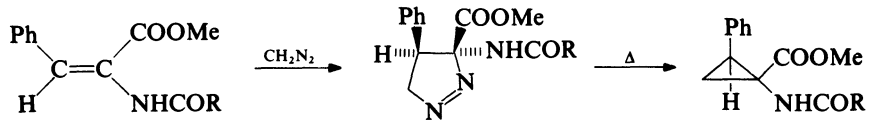
Thermolysis of pyrazolines was also used for aminocyclopropane synthesis. The corresponding starting materials were obtained from diazomethane and an alkene bearing a suitable nitrogen functional group, e.g. an amido or azido moiety.

Thus, 1,*N*-diacylenamines like **275** underwent a [2+3] cycloaddition with diazomethane. The resulting pyrazolines (**276**) gave thermal ring contraction to aminocyclopropane derivatives[34,289,383–387]. These reactions have been used in order to synthesize cyclopropyl amino acids. Recently, Stammer and coworkers[387] outlined an elegant way for the formation of cyclopropylogous amino acids (**278**) by starting from N,O-protected serine (**274**) (Scheme 9). The aminocyclopropane carboxylic acids (**278**) were obtained via the intermediate products (**275–277**). Compounds **278**, isolated in good yields, were reported to have *E*-configuration[387] (e.g. coronamic acid, **278**, R = Et).

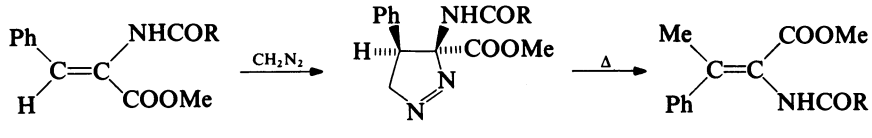


SCHEME 9

Two different pathways were observed for the pyrolysis of the diastereomeric cycloadducts **280** and **283**[388]. While *E*-isomer **280** gave cyclopropane **281** (equation 60),



(279) (280) (281) (60)

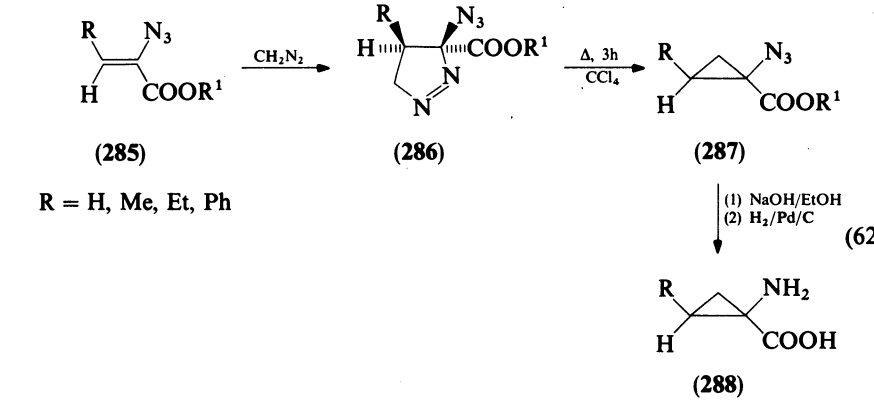


(282) (283) (284)

(61)

the corresponding *Z*-isomer **283** decomposed to an olefinic compound **284** (equation 61).

288, the diastereomer of **278**, could be obtained with high selectivity by cycloaddition of diazomethane to the vinyl azide **285**[389,390] (equation 62). Ring contraction of the primary



(285) (286) (287)

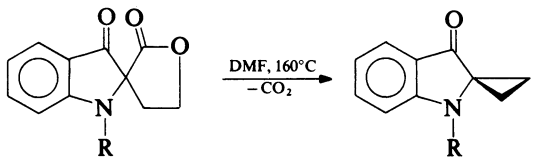
R = H, Me, Et, Ph

(62)

(288)

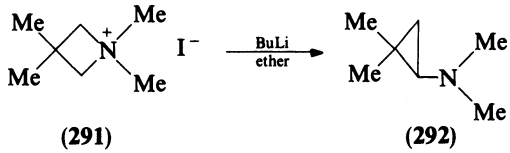
product (**286**) and conversion of the azido moiety in **287** to an amino function led to **288**[389,390]. The stereoselectivity in the synthesis of **288** depended on the substituent R. R = Me generated a 4:1 mixture of diastereomeric azides (**287**), whereas R = Et or R = Ph yielded pure azide isomers (**287**)[390].

Further examples of aminocyclopropane formation by a ring contraction reaction are shown in equations 63 and 64[29,391]. The generation of **292** (1% yield) in a Stevens rearrangement from **291** is of interest only from a mechanistic point of view[29].



(289) (290)

(63)

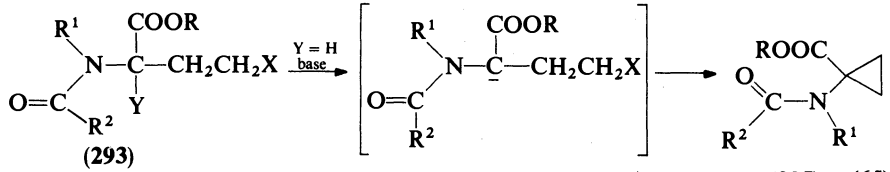


(291) (292)

+ other products. (64)

4. *Miscellaneous starting materials*

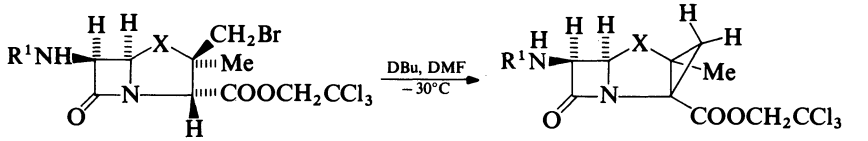
Acylamino acids (**293**) with a leaving group in the γ-position reacted with bases to yield aminocyclopropanecarboxylic acid derivatives (**295**)[392–396] (equation 65). A sulfonium



(**293**) (**294**) (**295**) (65)

$X = Hal, \overset{+}{S}Me_2, \overset{+}{N}Me_3$

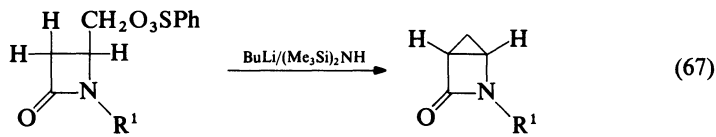
moiety as a leaving group in this reaction[392–394] corresponds to the biosynthesis of aminocyclopropanecarboxylic acid. Intermediate **294** could also be generated from a diester (**293**, Y = COOR) by a partial saponification and decarboxylation[397]. 2,3-β-Methylenepenams (**297**) were accessible by a 1,3-elimination from bromo compounds (**296**)[398] (equation 66). Special reaction conditions diminished drastically the formation of side products as cephem or vinylthiazole derivatives. Reaction of β-lactam (**298**) to give



(**296**) (**297**) (66)

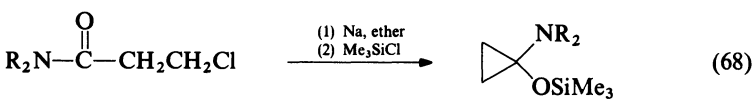
X = S, SO; $R^1 = PhCH_2CO$

bicyclic compound **299** represents a 1,3-ring-closure with a β-standing amino moiety (equation 67)[399]. Cyclothymine derivatives were accessible by a similar way (generation of the anion by deprotonation[399a], addition of cyanide[399b,c] to a double bond). An aziridinomoiety with a β-standing leaving group also could induce a 1,3-ring-closure[399d].



(**298**) (**299**) (67)

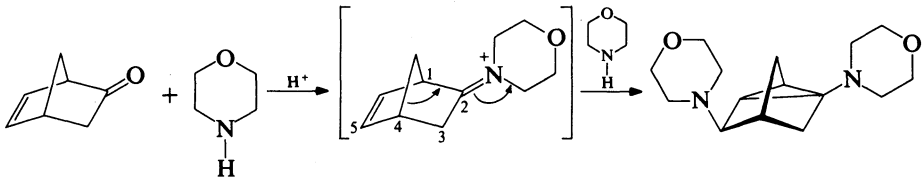
Wasserman and Dion reported an easy preparation of a siloxy derivative of an aminocyclopropane (**301**), namely by treatment of β-chloropropionic amide (**300**) with sodium and trimethylsilyl chloride[400] (equation 68). Because of the simple displacement of



(**300**) (**301**) (68)

the siloxy group in **301** by other substituents, this reaction outlines a convenient approach to aminocyclopropane chemistry.

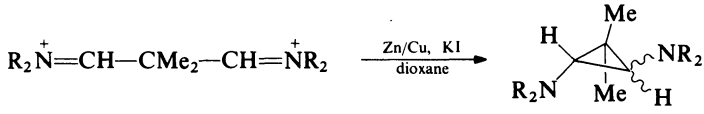
A 1,3-ring-closure to an aminocyclopropane was also observed during the reaction of the norbornenone **302** with morpholine (equation 69). In the presence of *p*-toluenesulfonic



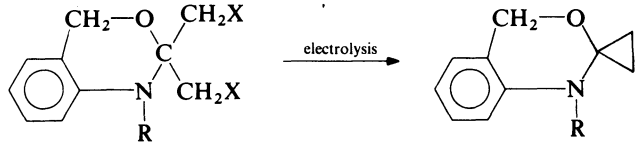
(302) **(303)** **(304)** (69)

acid, the diamine (**304**) was obtained in 23% yield[401,402]. Its formation results from addition of morpholine at C(5) of the cationic intermediate (**303**). The same reaction without acid catalysis is more complex[401,402]. A similar formation of nortricyclenes with an aminocyclopropane structure was described for the reaction of norbornenones with anilino derivatives[403] or hexamethyleneimine/$HClO_4$[404].

The aminocyclopropanes in equations 70 and 71 are formed by reductive processes[202,405]. Electrolysis of **307** (X = Cl) gave **308** in 10% yield[202]; this represents a less common type of aminocyclopropane synthesis by a 1,3-ring-closure. For a reductive formation of diaminobarbaralanes see Ref. 405a.



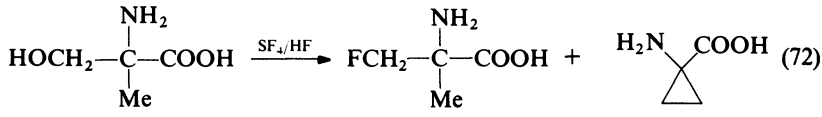
(305) **(306)** (70)



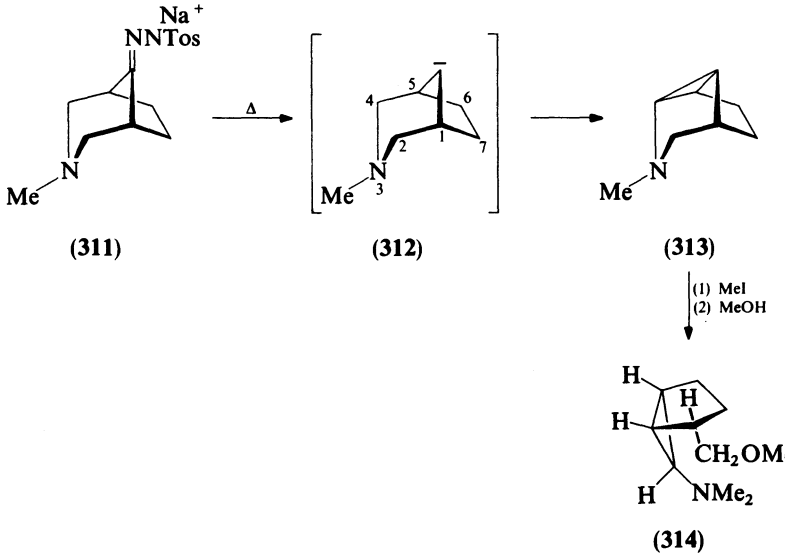
(307) **(308)** (71)

X = Cl 10%; X = Br 0%

The formation of aminocyclopropanes **6** and **313** is based on an insertion reaction into a γ-CH bond by a cation[406] (in the case of **6** or a carbene (**312**)[407] (equations 72 and 73). The



(309) **(310)** **(6)** (72)

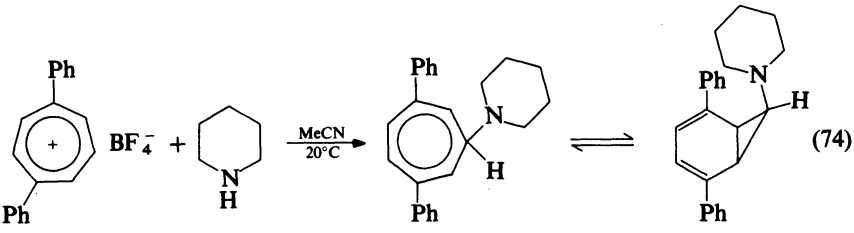


(311) (312) (313) (314) (73)

cation was generated from **309** by SF_4/HF; besides the aminocyclopropane **6** (28% yield), the normal substitution product **310** was obtained[406].

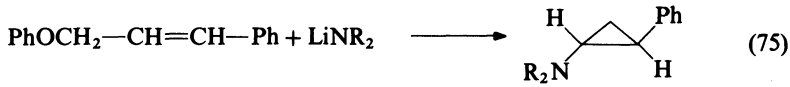
The tosylhydrazide **311** led to the aminocyclopropane derivative (**313**) in 56% yield upon heating[407]. Alkylation of **313** and methanolysis of the ammonium salt yielded the aminocyclopropane (**314**). This access to an aminocyclopropane by a carbene insertion only partially could be extended to similar starting materials[407, 407a].

Norcaradiene formation from a cycloheptatriene corresponds to a 1,3-ring-closure. On the basis of this reaction, aminocyclopropane **317** was obtained as a solid in 94% yield from piperidine and the tropylium ion **315**[408] (equation 74). A rapid equilibrium between **316** and **317** was postulated in solution. Electrocyclic 1,3-bond connections also were involved in the fluctual behaviour of 9-azabarbaralanes[408a–c], in the formation of homoazepines (from nitrenes and cycloheptatriene[408d–f]) and in a 6-azabenz[10]annulene system[188e].



(315) (316) (317) (74)

Addition of a lithium amide to the propenyl ether **318** gave **319** in 38–73% yield[409] (equation 75). A phenyl group in **318** was necessary to produce the aminocyclopropanes (**319**) presumably by its stabilizing effect on the intermediate carbanion.

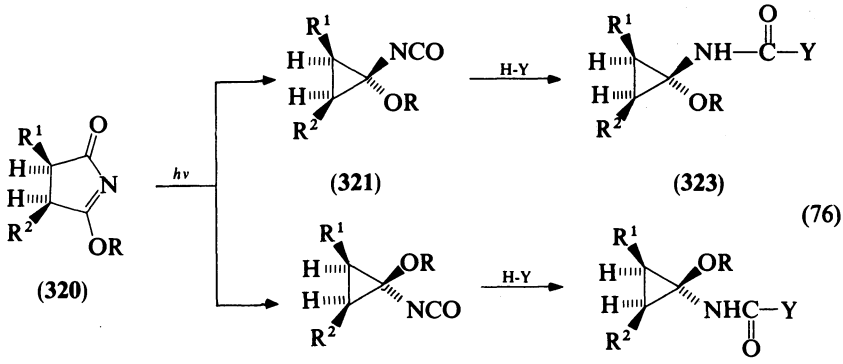


(318) (319) (75)

D. Formation of Aminocyclopropanes by Photoreactions

1. Pyrrolinones as starting materials

Koch and coworkers reported an efficient synthesis of alkoxy aminocyclopropane derivatives by the photolysis of alkoxypyrrolinones (**320**)[410–415]. The primarily formed isocyanates (**321**/**322**) were converted into urea or urethane derivatives (**323**/**324**) (equation 76). Pyrrolinone photoreaction was shown to be a very convenient basis for the

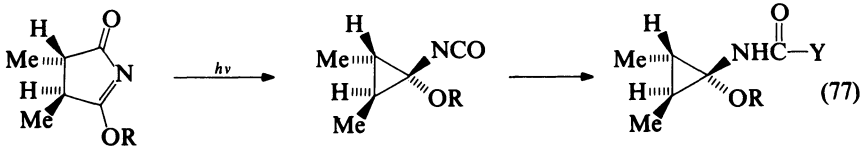


(320) (321) (322) (323) (324) (76)

$R^1 = R^2 = H, Me$
$R^1R^2 = (CH_2)_{2-4}$

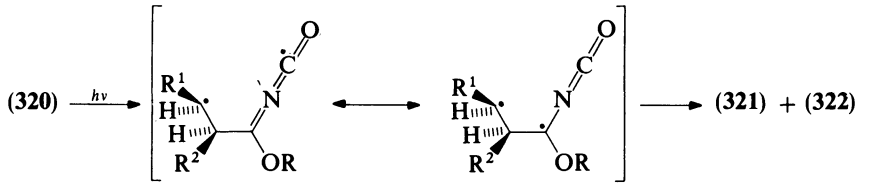
H-Y = R^3OH, R^3_2NH

preparation of coprine[416]. The *cis* and *trans* configuration of the pyrrolinone substituents **320** ($R^1 = R^2 = Me$) and **325** (equation 77) remained unchanged at least to 98% during



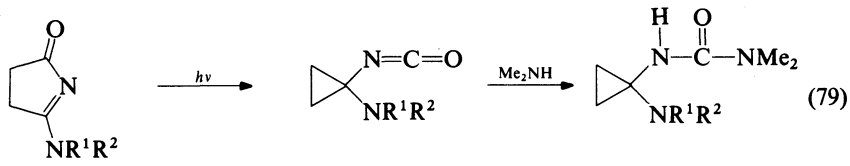
(325) (326) (327) (77)

ring-contraction[413]. On the other hand, the O,N-acetal group was not formed in a stereospecific way: **320** ($R^1 = R^2 = Me$) led to a *syn*/*anti* mixture **321**:**322** = 3.3:1[413]. Similarly, bicyclic pyrrolinones (**320**, R^1, $R^2 = -(CH_2)_{2-4}-$) generated *endo*/*exo* mixtures from which pure *exo*-aminocyclopropanes (**324**) could be isolated[412,414]. The photolysis of **320** was explained as a Norrish type I reaction leading to a σ, π-type diradical (**328**) (equation 78). Internal rotation around the C–C bond in **328** prior to ring-closure took place only to a very small extent, as shown by stereochemical investigations with **320** and **325**[413].



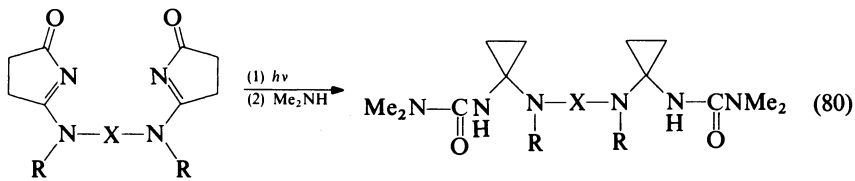
(328) (78)

Photolysis of aminopyrrolinones (**329**) also led to aminocyclopropane derivatives (**330**) which were transferred into the urea derivatives (**331**)[417] (equation 79). Cyclopropanes



(329) (330) (331) (79)

330 or **331** from pyrrolinones possessing a primary amino moiety (R^1 = H) were obtained only in low yields probably because of tautomerization of **329** or polymerization of **330** (R^1 = H). A twofold photoisomerization of a bis-pyrrolinone (**332**) was only successful when the two heterocyclic systems were spatially separated by a rigid bridge. This was the case for X being a butyne, butene or xylene unit but not a 1,2-dialkyl moiety[417,418] (equation 80).

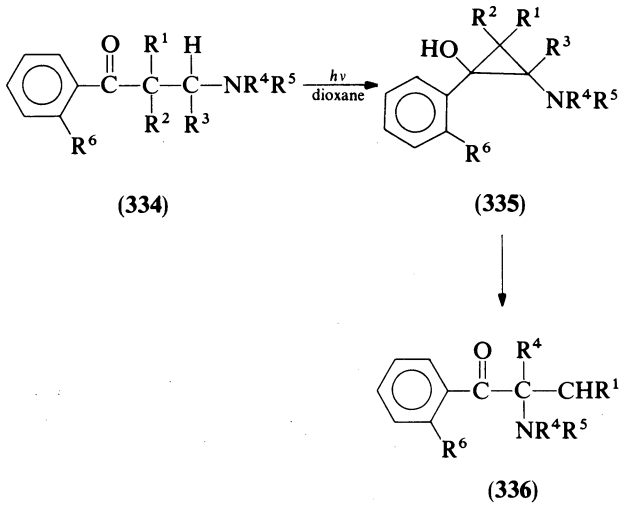


(332) (333) (80)

2. Amino ketones as starting materials

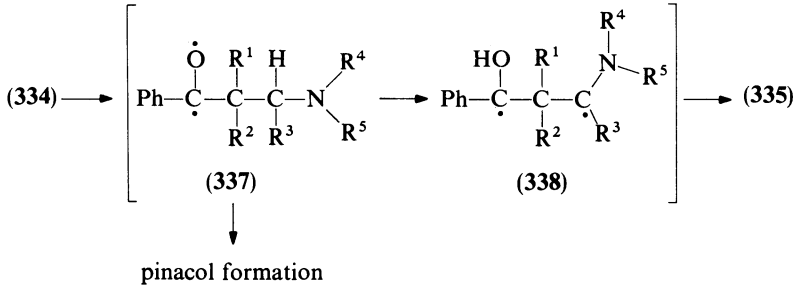
An easy preparation of 1-amino 2-hydroxycyclopropanes (**335**) in very good yields was found by Roth and his group by irradiation of ω-amino propiophenones (**334**)[419–424] (equation 81). Cyclopropane formation required starting materials **334** with at least one alkyl or aryl group in the 2- or 3-position. Unsubstituted propiophenones (**334**, $R^1 = R^2 = R^3$ = H) reacted preferentially to give pinacol derivatives. Morpholine as amino function gave the best results, but other amines sometimes failed to yield aminocyclopropanes (**335**). This was not due to the failure of the photoreaction but was a consequence of a subsequent ring-opening.

Especially a phenyl group in 2-position of **335** led to **336** by ring-opening, when NR_2 was a strongly electron-donating group, like dimethylamine, pyrrolidine or hexahydroazepine. For the synthesis of **335** from secondary amines (**334**, R^4 = H), the absence of any hydrogen in the 2-position (i.e. R^1, $R^2 \neq$ H) was essential by preventing a



(334) (335) (336) (81)

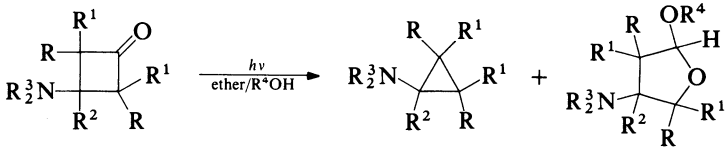
photodehydrogenation or a photopinacolization. Photocyclization was also successful with an *N*-acylated bicyclic derivative (**334**, R^2, $R^6 = -(CH_2)_2-$)[425]. The biradicals **337** and **338** were discussed as intermediates in the photochemical cyclopropanation (equation 82); the configurations of the products were not established.



(334) (337) (338) (335) (82)

pinacol formation

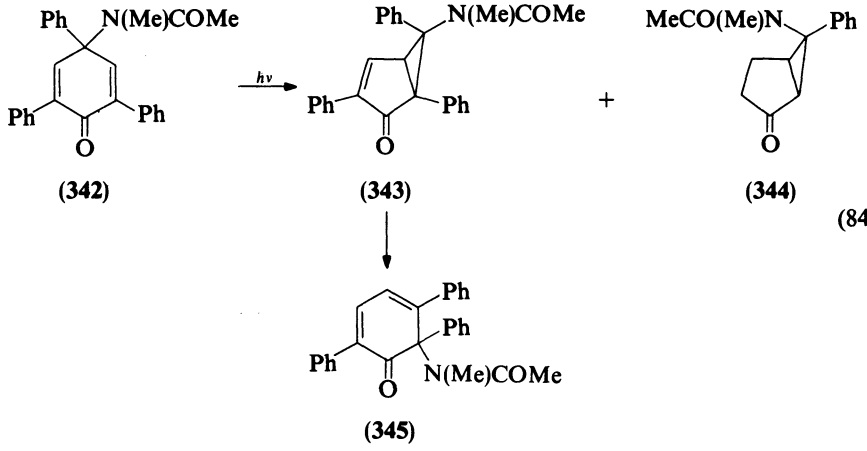
Irradiation of an aminocyclobutanone (**339**) in ether in the presence of water, methanol or phenol yielded a mixture of **340** and **341** in about equal amounts[426]. **341** resulted from an addition of R^4OH in the course of the photoreaction (equation 83).



(339) (340) (341) (83)

3. Amino-substituted dienes as starting materials

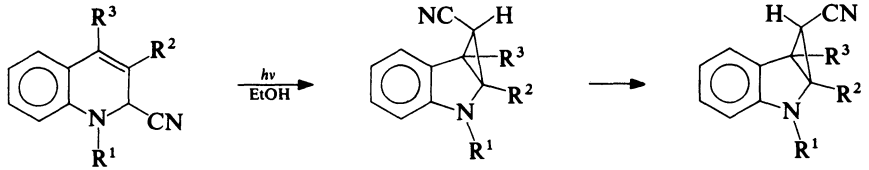
Photolysis of the aminodienone **342** gave compounds **343–345**[427] (equation 84). Pure aminocyclopropane derivative (**343**) was isolated in 17% yield by chromatography. **343** isomerized into **345** upon heating in benzene.



(342) (343) (344) (345)

(84)

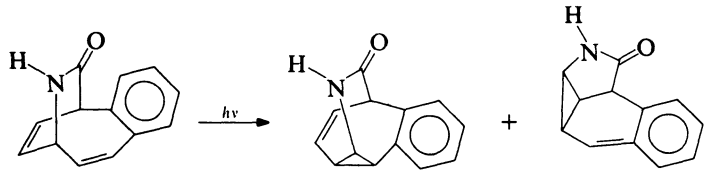
Dihydrochinolines **346** and **347** gave in most cases stereospecifically *endo*-cyano homoindoles (**348**) upon irradiation in ethanol (equation 85)[428a-g]. **348** could be equilibrated to a **348/349** mixture upon irradiation in acetone, by heating or by treatment with BF_3. An aminocyclopropane derivative was reported to be a side product of the photoaddition of amines to benzene[428f].



(346) R^1 = COOR
(347) R^1 = COR
(348) (349)

(85)

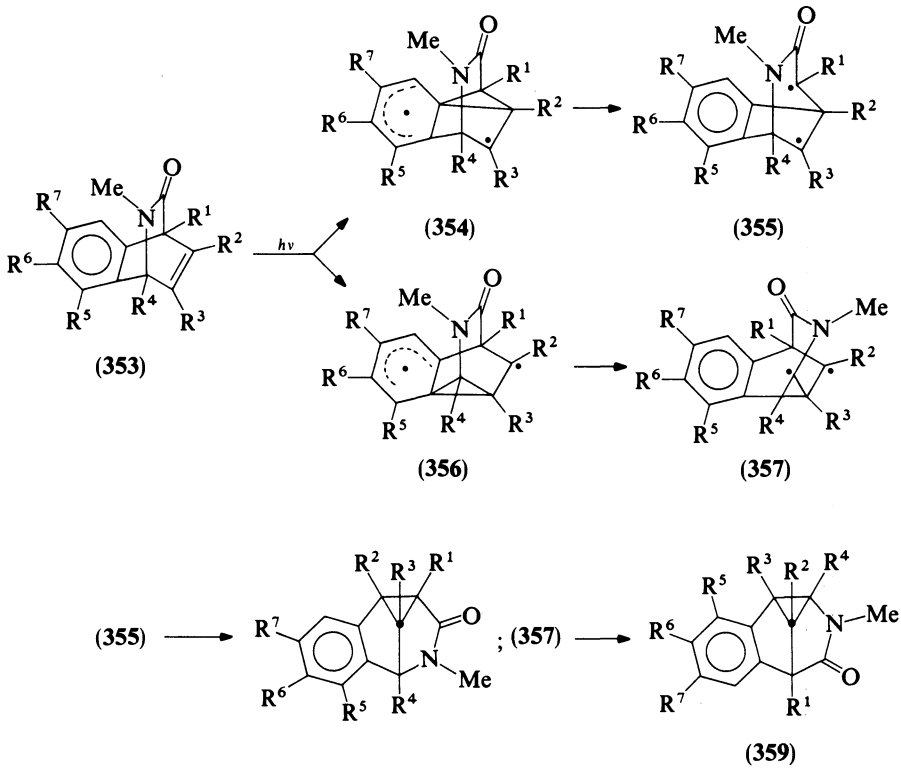
The diene system in **350** afforded the aminocyclopropanes **351** and **352** in a 1:3 ratio upon sensitized irradiation[429-431] (equation 86); direct photolysis decreased the percentage of **352**. Using specifically deuterated compounds, it was found that either a di-π-methane or a $\pi 2a + \pi 2a$ rearrangement were involved. However, it was not possible to distinguish between both pathways[431].



(350) (351) (352)

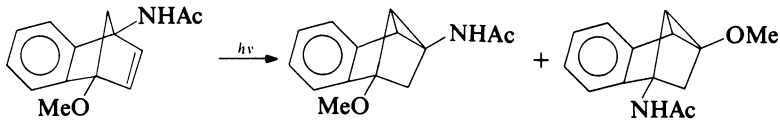
(86)

Instead of the amide (**350**), the corresponding methyl imidate also could be used for the photoreaction. In this case, the labeling studies uniquely identified the process as a di-π-methane rearrangement with initial vinyl-to-vinyl coupling[429-431].



SCHEME 10

Similar di-π-rearrangements were described for the photoisomerization of benzo-2-azabicyclo[2.2.2]octadienones (**353**)[432-436] (Scheme 10) and benzonorbornadienes (**360**)[437] (equation 87). Irradiation of **353** (R^1–R^7 = H) in acetone generated a 25:75 mixture of **359** and **358**[432].

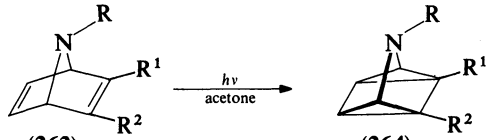


(360) (361) (362) (87)

The selectivity of the formation of the radicals **354**/**355** and **356**/**357** is strongly affected by the substituents R^1–R^7, especially R^2 as a phenyl substituent or R^5 as a cyano, or a methoxy moiety increased the yield of **359** by stabilization of the radical intermediates **356**

and **357**[433, 434]. Photochemical behavior of the corresponding imidates was investigated too[435]. Aminocyclopropane derivative **361** resulted as well as 38% of **362** from acetophenone-sensitized photoisomerization of **360**[437] (equation 87).

Various bicyclic compounds with an aminocyclopropane structural unit (azaquadricyclanes[438a-e], azabarbaralanes[408a, c] or azaprismanes[438f-h]) were obtained by photochemical cyclization of suitable precursors with CC double bonds (e.g. **363** → **364**) or a CC double bond and an aziridino moiety[438j, k].

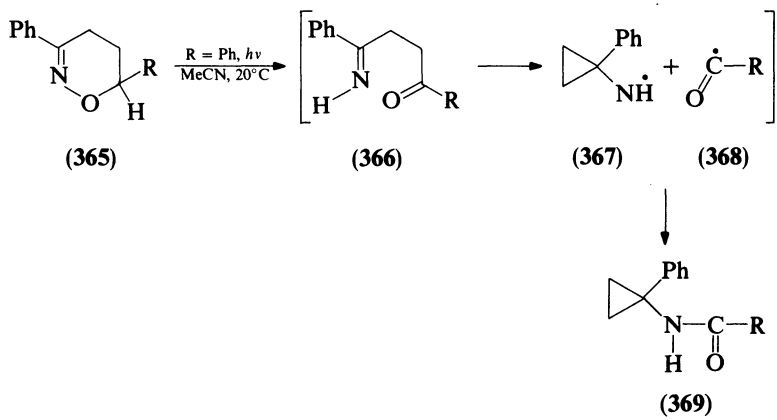


(88)

R = Tos, Ac **(363)** **(364)**

4. *Miscellaneous starting materials*

Formation of an aminocyclopropane (**369**) in 28% yield in addition to other products was observed in the photoreaction of **365**[439] (equation 89). A phenyl substituent (R = Ph)



(365) **(366)** **(367)** **(368)** **(369)**

(89)

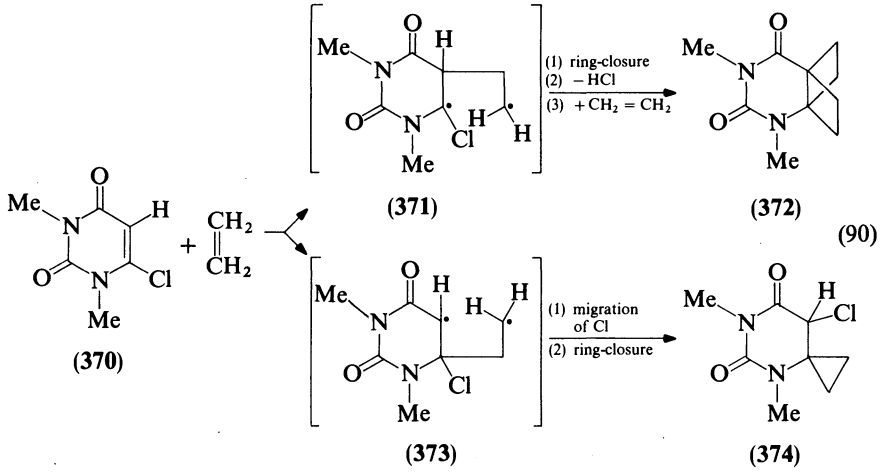
was necessary for cyclopropane generation; with other substituents, the reaction failed. Intermediates **366** and **367/368** were invoked to explain the formation of **369**.

The aminocyclopropane derivative **374** and the propellane **372** were obtained, each in 26% yield, by photocycloaddition of **370** and ethylene in acetone[440]. Diradicals **371** and **373** were suggested as intermediates in the photoreaction (equation 90). The use of isobutene or 2,3-dimethyl-2-butene instead of ethylene gave no cyclopropane product[440].

E. Aminocyclopropanes from a Three-membered Ring containing a Nitrogen Function

1. *Nucleophilic substitution at aminocyclopropane derivatives*

Aminocyclopropanes bearing a suitable leaving group in the α-position have been extensively used for the synthesis of further aminocyclopropane derivatives. Thereby, an amino, a hydroxy, a methoxy or a trimethylsilyloxy moiety in **375** could be displaced by other substituents leading to **377**. Acidic medium or a large excess of the nucleophile (as in solvolysis reactions) or activation of the leaving group (e.g. by quaternization of an amino

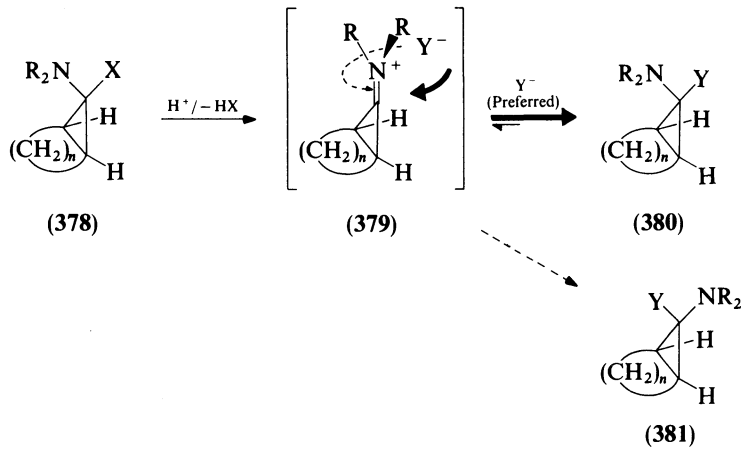


(370) (371) (372) (373) (374) (90)

moiety[345, 441–443] or by esterification of –OH by $TiCl_4$[400]) facilitated the substitution. A ring-opening as a consequence of the substitution was reported only in special cases[342, 348, 368, 443, 444]. α-Chlorocyclopropylamines (**375**, X = Cl) were preferentially used as starting materials if the amino moiety in **375** had poor electron-donation character (e.g. R^1R^2N = NHAcyl)[319].

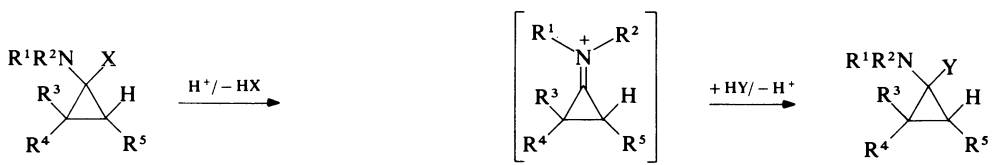
Reactions of **375** with carbon acids in the sense of a Mannich reaction are useful for the generation of a bond between carbon and a cyclopropane moiety, but only few carbon acids reacted with monocyclic compounds without difficulties in this way[451] (see also Ref. 443). Similar failures have not been observed with bicyclic systems using aminals (**375**, $\dot{X} = NR^1R^2$) or enaminosulfonium salts (**258**) [**258** → **272**, Scheme 8] as starting materials.

The synthesis of aminobicyclo[n.1.0]alkane derivatives by nucleophilic substitution normally led to compounds **380** in which the nucleophile Y is in the *exo*-position[17, 18, 58, 341–343, 348, 355–359, 363, 369, 371–374, 377, 379–381, 443, 444, 446, 448, 453–455]. This is the consequence of the intermediacy of a bicyclic iminium ion (**379**) which is preferentially attacked from the less hindered *exo*-position (equation 91). If, additionally,

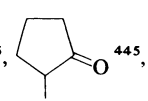
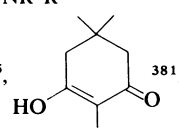
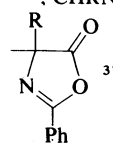
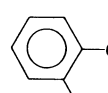


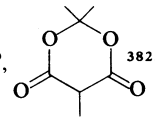
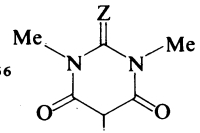
(378) (379) (380) (381) (91)

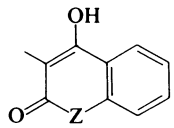
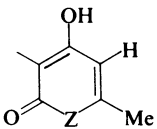
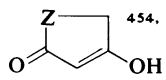
TABLE 2. Synthesis of aminocyclopropanes from other aminocyclopropane derivatives



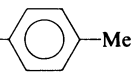
(375) (376) (377)

Alkyl$_2$N or 	X = NR_2	→ Y = OH[204, 342, 343, 360, 363, 369], OR[348, 359, 360, 369, 379, 441, 445], SR[372], SH[446], H[17, 18, 58, 341, 342], NR^3R^4 [193, 358, 363, 378, 443], $CHRNO_2$[442, 447], CH_2COR[445],  [445],  [381],  [373, 448], CN[359, 363, 380], N = NR[373]
	X = OH	→ Y = NR^3R^4 [195, 198, 199, 449], CN[449, 450], OR[204, 449], SR[449], N_3[449], *N*-heterocycles[400], $CH(CO_2Me)_2$[400, 451], Z—  (Z = NR_2)[195, 400], CH_2COMe[445, 451],  OH[451, 452]

X = OMe → Y = alkyl, aryl[359, 377, 379],  [382, 456]  [382, 453],

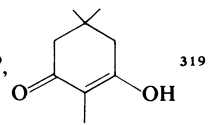
 [454],  [454],  [454, 455, H[348, 359]

X = $OSiMe_3$ → Y = OH[400], alkyl, aryl[400], CN[450], CH-acids[455]

X = O_2S–  –Me → Y = OH[203, 319]

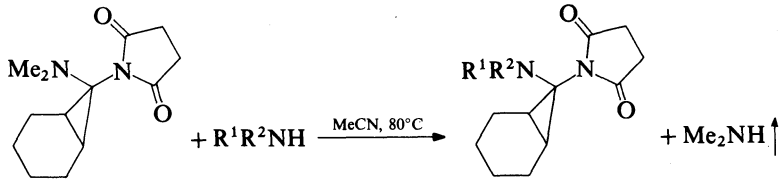
Acyl–N(H)–

X = OH → Y = Cl[319]

X = Cl → Y = OR^{319}, SR^{319}, NR^3R^4 [319], O_2SR^{319},  [319]

the added nucleophile is a good leaving group and is not bulky, the primary product, (**380**), isomerized to the thermodynamically more stable *exo*-amino derivative **381**[342, 343, 363] (see also Section II.C.2). The isomerization occurred at higher temperatures in the presence of an acid. Thus, depending on the reaction conditions, both diastereomers **380** and **381** could be obtained in good yields in a pure form when Y is a hydroxy[360, 369, 371], methoxy[360, 369, 371], Meldrum's acid[382] or barbituric acid[453] moiety.

Compounds **384** were prepared from **382** and secondary[358] or primary[590] amines (**383**) in boiling acetonitrile (equation 92). This unexpected substitution of an *endo*-amino



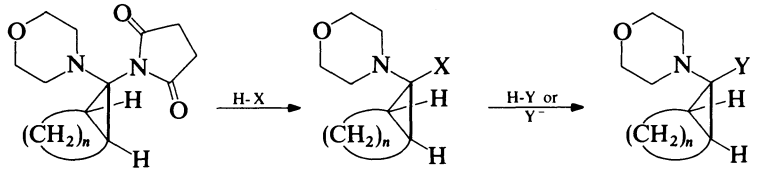
(92)

(**382**) (**383**) (**384**)

function with retention of configuration was shown to be the consequence of a combination of an isomerization and two substitution processes (both taking place in the *exo*-position).

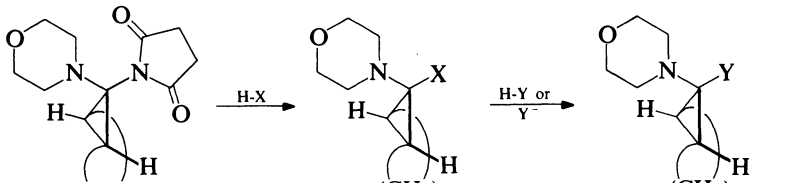
The stereochemical course and the result of all of these reactions with bicyclic compounds are best monitored by the ^{1}H-NMR signals of the nitrogen heterocycle (for the stereoindicator function of the heterocycle see Section II.C.2).

Cis- and *trans*-aminals **385** and **230** which could easily be obtained from enaminosulfonium salts (**255**) (Scheme 7) or chloroenamines (**228**) (see equation 54) were used for the preparation of further sterically pure aminocyclopropanes (equations 93 and 94).



(93)

(**385**) (**386**) (**387**)

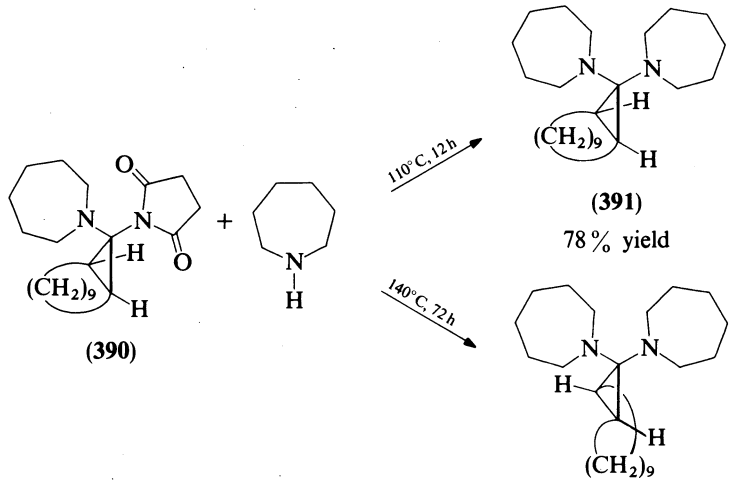


(94)

(**230**) (**388**) (**389**)

X =  → Y = CN; X = OMe → Y = H, alkyl or HY = Carbon acid

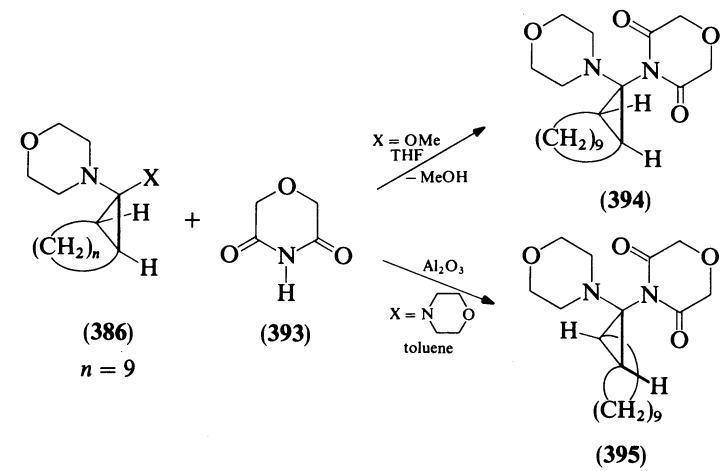
Normally *cis–trans* isomerizations were not observed during the substitution[348, 372, 373, 378–381, 444, 446, 448, 454–456] (see equations 93 and 94). In contrast, either a *cis*- or a *trans*-aminal, **391** and **392**, could be synthesized as the pure isomer in good yields by the reaction of **390** with hexahydroazepine (equation 95). Higher temperatures



(**390**) (**391**) 78 % yield (**392**) 61 % yield (95)

and a longer reaction time caused isomerization in this substitution[359]. No isomerizations occurred, however, in other substitution reactions of **391** and **392** at room temperature according to equations 93 and 94[359, 456].

Another example of *cis–trans* isomerization was found in the reaction of the *cis*-aminal **386** (X = morpholine) with imide **393** in boiling toluene when morpholine was removed with Al_2O_3 in a Soxhlet apparatus[444]. Thus, pure **395** was isolated in 36 % yield, whereas

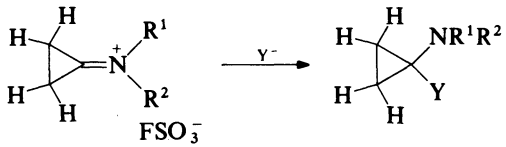


(**386**) *n* = 9 (**393**) (**394**) (**395**) (96)

the corresponding *cis* compound (**394**) was obtained from **393** and the *cis*-O,N-acetal **386** (X = OMe) under milder conditions (equation 96)[444].

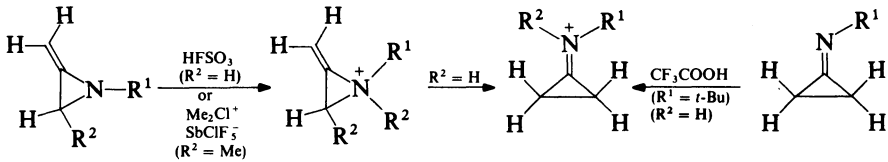
2. *Addition of nucleophiles to cyclopropaniminium salts or cyclopropanimine isomers*

Cyclopropaniminium salts **376**, **379** and **396** are intermediates in the nucleophilic substitution of aminocyclopropane derivatives. Salts **379** or **396** were prepared in solution from suitable precursors[345, 346, 363, 441, 443, 452]. Addition of nucleophiles such as MeO^-, PhO^-, PhS^-, succinimide anion, or carbanions gave the aminocyclopropanes (**397**)[441, 443] (equation 97). Sodium phenolate was alkylated at the oxygen atom by **396**[443] (for a *C*-alkylation of phenol by **375** (X = OH) see Table 2, Refs 451, 452).



(**396**) (**397**) (97)

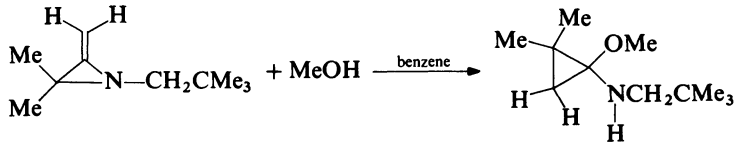
Cyclopropaniminium salts (**396**) also result from protonation of cyclopropanimines (**400**)[457] or from protonation or alkylation of methyleneaziridines (**398**)[443, 458, 459] (equation 98). In the latter case, the primarily formed aziridinium salts (**399**) rearranged



(**398**) (**399**) (**396**) (**400**)

ring-opening reactions (98)

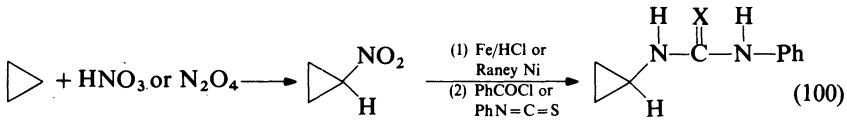
upon warming into the salts (**396**); according to these isomerizations, an aminocyclopropane (**402**) could be obtained from the methyleneaziridine (**401**) and methanol (equation 99). The formation of products from the nucleophile and an allyl cation derived from **396** were also reported[457, 459, 460]. In these cases the temperature required for the isomerization of the precursor to **396** already caused a subsequent ring-opening reaction of **396**.



(**401**) (**402**) (99)

3. *Interconversion of the nitrogen functional group*

Reduction of nitro compounds—a standard preparation for amines—was also applied to nitrocyclopropane (**404**)[178] (equation 100). Low yields of **404** from the nitration reaction of **403** represent a handicap of this access to aminocyclopropane.

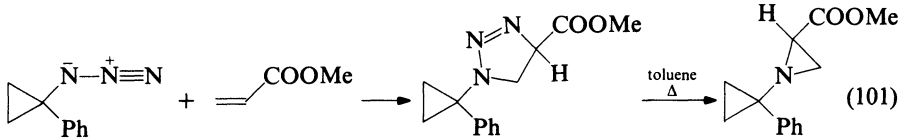


(100)

(**403**) (**404**) (**405**)

X = O, S

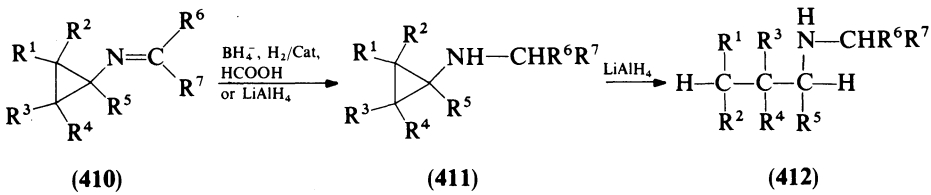
A special aminocyclopropane (**409**) could be prepared by cycloaddition of azide (**406**) with compound **407**[461] (equation 101) (see also Section II.A.2.b; for an easy preparation of cyclopropyl azides see Ref. 218).



(101)

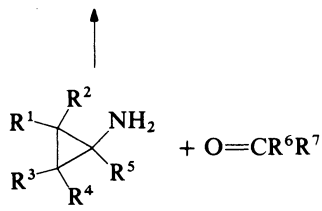
(**406**) (**407**) (**408**) (**409**)

Imines (**410**) could be reduced to aminocyclopropanes by borohydrides, e.g. Refs 462–473, catalytic hydrogenation[463, 473–476] or formic acid[25, 29, 38, 86, 92, 149, 327, 477] (equation 102). In general, lithium aluminium hydride as reducing reagent led directly to ring-opening products (**412**)[462–464]. Shorter reaction times, however, also allowed the isolation of **411** from **410** and $LiAlH_4$ in good yields[463]. Reduction of **410** to **411** has often been used for alkylation of the amino group in **413**. In these cases, e.g. Refs 464–477, imines (**410**) were only intermediate products on the way from **413** to **411**.



(**410**) (**411**) (**412**)

(102)

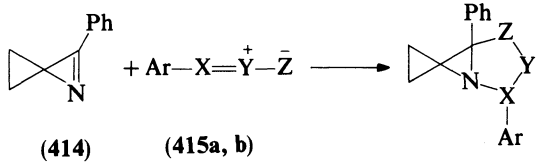


(**413**)

Interconversion of an imino functional group into an amino moiety by hydrolysis is part of those aminocyclopropane syntheses in which an imino, imidato, thioimidato or amidino

compound is used as starting material (see equations 41–44, 50 and Schemes 2 and 4).

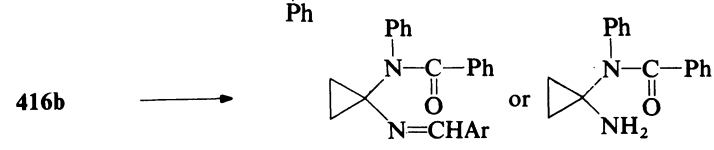
Cycloaddition of nitrone (**415b**) to the imino function in **414** gave aminocyclopropanes **417** or **418** as well as other products[478] (equation 103). The expected, primary product, **416**, was obtained from a nitrile ylide (**415a**) by a cycloaddition reaction[399].



(**414**) (**415a, b**) (**416a, b**)

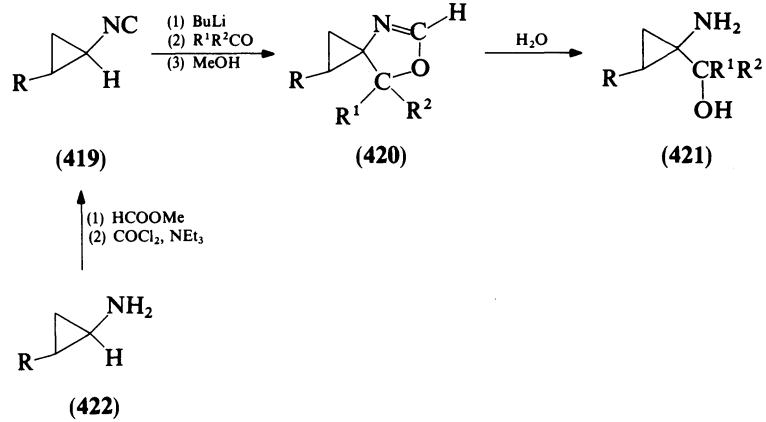
a: $X = \overset{+}{Y}-\bar{Z}=CH=\overset{+}{N}=\bar{C}-Ph$

b: $X = \overset{+}{Y}-\bar{Z}=CH=\overset{+}{N}(Ph)-O^-$ (103)



416b (**417**) or (**418**)

Isocyano and amino functions can easily be interconverted via the corresponding formamide. Thus, introduction of an alkyl group into the α-position of an aminocyclopropane (**422**) could be performed by alkylation of the corresponding isocyano compound (**419**) via **420**[479–481] (equation 104).



(**419**) (**420**) (**421**) (**422**) (104)

Further applications of an azido or an isocyano function as a masked amino moiety in aminocyclopropane synthesis are described in Section II.C.3 (equation 62 and Sections II.B.1.c and II.B.2.a (Scheme 3 and equation 50).

III. REACTIONS AND BIOCHEMICAL ACTIVITIES

Theroretical considerations, spectroscopic properties, chemical reactions and the biochemistry of aminocyclopropanes are discussed together with those of other cyclopropane

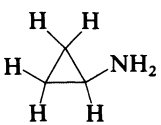
derivatives in several chapters of this book. Consequently further considerations of these facts would not be necessary. Especially discussion of theoretical and spectroscopic facts is only reasonable in comparison with other members of the cyclopropane family. Since this is not quite so for chemical reactions and biochemistry, these two topics of aminocyclopropane chemistry will be surveyed shortly in order to complete this review.

A. Reactions of Aminocyclopropanes

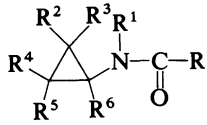
1. Reactions of the amino moiety

In general, the behavior of the amino moiety in **1** showed no great differences from that of alkylamines or other cycloalkylamines. Cyclopropylamine (**77**) ($pK_a = 9.10$[482]) was found to be somewhat less basic than isopropylamine ($pK_a = 10.67$[482]); further pK_a values for **77** and other aminocyclopropane derivatives are reported in Refs 347, 483–486. Interactions of **77** with *p*-fluorophenol[487, 488], propane-2-thiol[489], H^+ in the presence of 18 crown-6[490] or Ag^+[486] have been investigated. For considerations of the protonation of **77** in the gas phase see Refs 491–493. Different basicity was observed for NR_2 groups in the *exo*- and *endo*-position of a [3.1.0] bicyclic system[348].

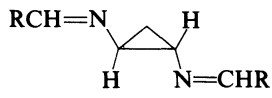
Aminocyclopropanes were easily acylated by acid chlorides, isocyanates or isothiocyanates (e.g. Refs 3, 24, 27, 36, 71, 80, 82, 125, 178, 179, 184, 224). Polyureas, polyurethanes or polyamides have been prepared from 1,2-diaminocyclopropane[57, 494]. Reduction of the carbonyl group in **423** by lithium aluminum hydride worked quite well for tertiary amides[67, 72, 464, 465, 473, 495]; longer reaction times effected a ring-opening in the case of a secondary amide (**423**, $R^1 = H$)[76, 474, 496] ($LiAlH_4$ reduction of secondary amides without ring-opening[16, 76, 495, 497]; use of B_2H_6 or B_2D_6 instead of $LiAlH_4$[496, 498]).



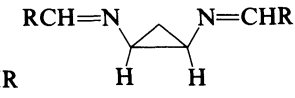
(77)



(423)



(424)

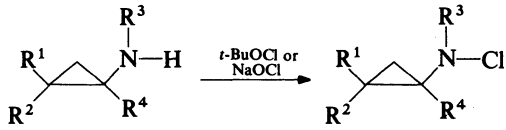


(425)

Alkyl halides or oxiranes have been used for alkylation reactions of **77** in most cases (for difficulties observed in alkylations see Refs 122, 474; for arylation by halogenonitrobenzene see e.g. Refs 499, 500). Sometimes introduction of an alkyl moiety was performed by means of aldehydes or ketones via imines (see Section II.E.3) or acyl halides via amides and a subsequent reduction reaction[16, 76, 464, 465, 473, 495, 497, 498]. Alkylation of a *N*-cyclopropanimine[38, 149] or -carboxamide[67] followed by reduction in some cases seemed to be superior to a direct double alkylation of the corresponding amine; for bisalkylations by a Leuckart–Wallach reaction see Refs 25, 29, 38, 86, 92, 149, 156, 327, 477.

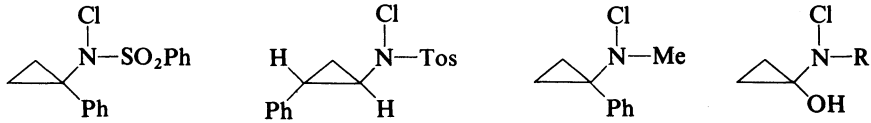
N-Monoalkylcyclopropylamines were obtained by alkylation of an *O*-benzylurethane or *N*-cyclopropyliminophosphorane and subsequent cleavage[501]. Ring formation by bisalkylation of 1,2-diaminocyclopropane is described in Refs 502, 503.

Preparation of bisimines from 1,2-diaminocyclopropanes and aldehydes required special conditions[49, 133, 279, 504–509]. *Trans*-1,2-bisimines (**424**) proved to be much more stable than the corresponding *cis*-1,2-bisimines (**425**), which could be obtained only for some definite groups R[506, 508]. For subsequent formation of diazepines or pyrroles from **424** or **425** see Section III.A.3.d. A similar ring-opening was observed in the reaction of 1,2,3-triaminocyclopropane with an aldehyde[49].



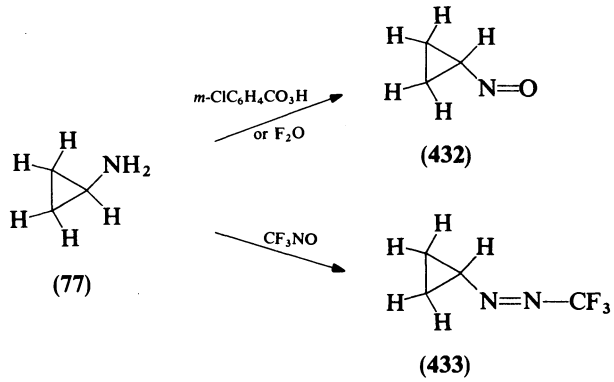
(426) (427) (105)

N-Chlorination of cyclopropylamines (**426**) was best performed by *tert*-butyl hypochlorite at low temperatures[194, 196, 197, 219, 447, 510] (equation 105); NaOCl was also used as chlorinating agent[511]. Some *N*-chlorocyclopropylamines (e.g. **428**) are stable compounds[511]; other derivatives such as **429** and **430** decomposed very rapidly in a ring-opening reaction[510, 511]. *N*-Chlorocyclopropylamines (**431**) played an important role in a ring-enlargement reaction to β-lactams[194, 196, 197, 219, 447] (see Section III.A.3.a).

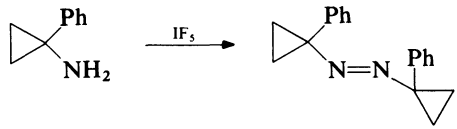


(**428**) (**429**) (**430**) (**431**)

Cyclopropylamine (**77**) could be oxidized to nitrosocyclopropane (**432**) by oxygen difluoride[512] or *m*-chloroperbenzoic acid[513] (equation 106). Azo compounds **433** and **435** were obtained by oxidation of **434** by IF_5[20] (equation 107) or condensation of **77** with a nitroso compound[514] (equation 106). Interconversions of an aminocyclopropane into an isocyano or azido cyclopropane are described, for example, in Refs 105, 479–481, 515, 516 and Refs 89, 461, 517, respectively. For formation of an *N*-cyclopropyl iminiophosphorane see Ref. 518. Nitrosation of *N*-cyclopropylurea derivatives was usually performed



(106)

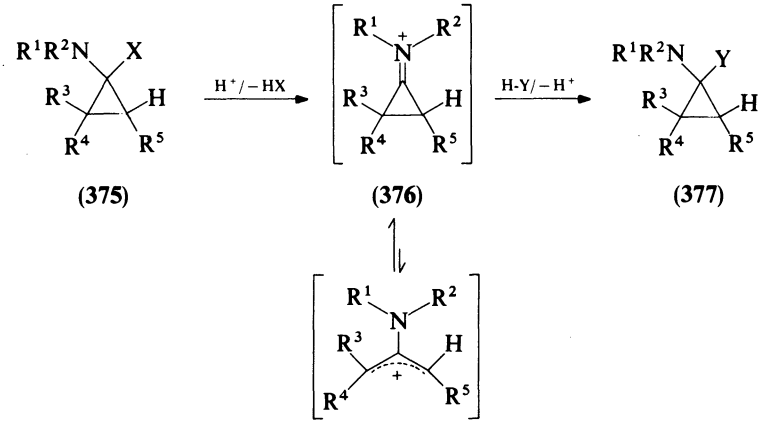


(**434**) (**435**) (107)

by $NaNO_2$/AcOH e.g. Refs 25, 28, 43, 69, 74, 83, 84, 99, 134 or N_2O_4, e.g. Refs 68, 69, 74, 85, 96, 97, 107, 108, 115, 117, 120, 121, 136, 138, 174. In some cases steric hindrance caused difficulties in preparing the *N*-nitrosourea derivatives, e.g. Refs 74, 110, 120, 139, 174.

2. *Nucleophilic substitution reactions*

Nucleophilic substitution of a leaving group X in **375** occurs very easily (equation 108). Normally, no opening of the three-membered ring is observed because of the greater

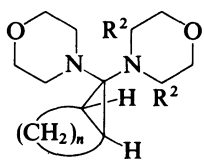


(375) **(376)** **(377)** (108)

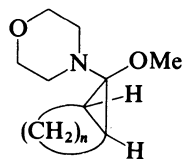
(436)

stability of the iminium intermediate (**376**) with respect to the amino allyl cation (**436**). **376** (R^1–R^5 = H) was calculated to be 33.5 kcal mol^{-1} [519] or 23.4 kcal mol^{-1} [520] lower in energy than **436** (R^1–R^5 = H). Alkyl substituents in the 2-position of **376**, e.g. **376** (R^1–R^4 = Me, R^5 = H), facilitated the formation of **436** with respect to the parent compound[346]. Cyclopropaniminium ions have been characterized by ^{1}H-[345, 346, 441, 443, 452, 457–459] and ^{13}C-NMR[363] spectroscopy or IR spectroscopy[345]. Preparative applications of nucleophilic substitutions according to equation 108 are listed in Section II.E.1 and Table 2.

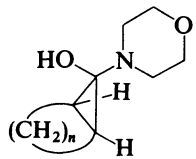
The steric course of the nucleophilic substitution at a [n.1.0]bicycle was investigated by using the deuterated compound **437**. The expulsion of the *exo*-morpholino group was favored by at least a ratio of 99 : 1[363, 444]. Depending on the nature of the nucleophile and the reaction conditions, either retention (e.g. formation of **438** from **437** and CH_3OH) or inversion (e.g. formation of **439** (n = 4, 9) from **437** (n = 4, 9) and H^+/H_2O) of configuration was observed.



(437, n = 4, 9)



(438)

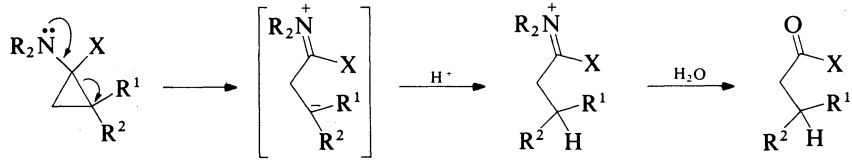


(439)

3. Ring-opening reactions

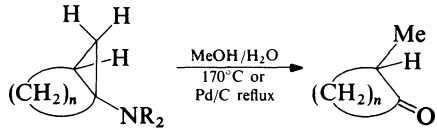
a. Opening of the vicinal cyclopropane C(1)–C(2) bond

Opening of the vicinal cyclopropane carbon–carbon bond in **440**, generating a zwitterion (**441**) makes **440** a homoenamine species. Compound **441** takes up a proton leading to **442**, which is readily hydrolyzed to a ketone (**443**) (equation 109). In general



(**440**) (**441**) (**442**) (**443**) (109)

aminocyclopropanes are stable towards acids[40, 42, 45, 270, 277] and therefore opening of the vicinal carbon–carbon bond in **440** required high reaction temperatures. Thus aminobicyclo[n.1.0]alkanes (**154**) were cleaved to yield ketones (**444**) in methanol–water at 170°C or by refluxing for 1–2 days in the presence of Pd/C[240, 270] (equation 110) (see also Ref. 521). Preparation of **154** from an enamine and a carbene and transformation of **154** into **444** represent an alkylation of a ketone, which was claimed to be superior to a direct enamine alkylation from a preparative point of view[270].



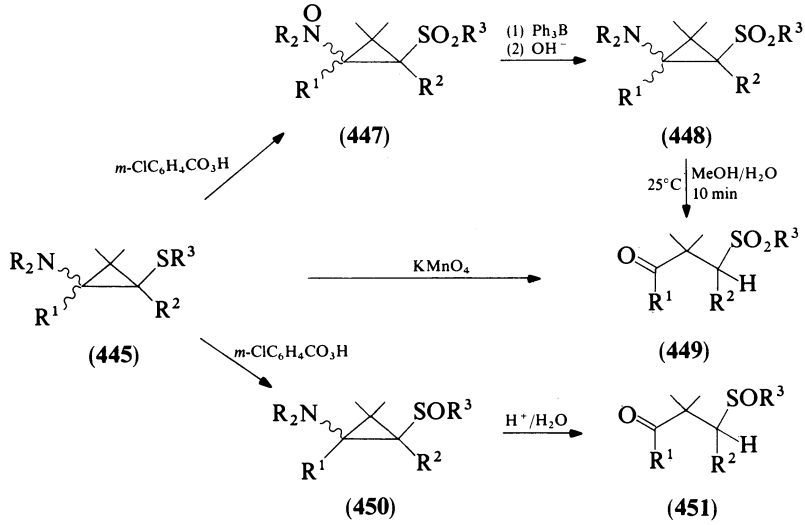
(**154**) (**444**) (110)

Ring-opening reactions can be facilitated by several influences: acceptor groups such as an acyl[94, 234, 235, 239, 241, 281, 357], sulfinyl[522] or sulfonyl[256, 523] moiety accelerate the homoenamine reaction by stabilization of the anionic part in **441**. Thus oxidation of the sulfido group in **445** to a sulfinyl or sulfonyl moiety led to compounds **448** and **450** which are less stable to ring-opening[256, 522, 523]. Sulfone **448** especially, could be obtained only by a special procedure via amine oxide **447**; oxidation of **445** by $KMnO_4$ gave product **449**[256] directly (Scheme 11).

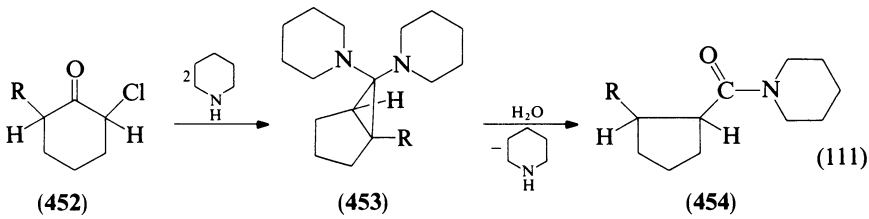
Ring-opening reactions of 2-phenyl- or 2,2-diphenylcyclopropylamines (Ph stabilizes the zwitterion **441**) are described in Refs 102, 233, 234, 240, 275, 332, 474, 524–526. For example, the influence of a 2-phenyl substituent upon ring-opening is demonstrated by the interaction of piperidine with chloroketones **452a** and **452b**. While unsubstituted chloroketone **452a** and piperidine gave aminal **453**, the analogous reaction of the phenyl-substituted chloroketone, **452b**, led to amide **454** as isolable product[527] (equation 111). The sequence **452** → **454** represents a special type of Favorskii reaction.

Formation of **455** from **122** and nucleophiles H–X already at room temperature demonstrates the influence of strain on the opening of the vicinal bond[224] (equation 112). Strain should also be the reason for ring cleavage of apotricyclyl amine (**597**) by water[22].

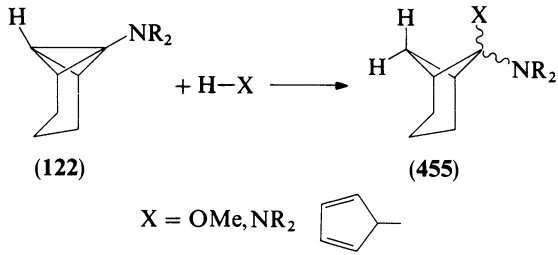
The donor substituent at C(1) plays an important role in the homoenamine reaction, too. Replacing morpholine (weaker donor) by pyrrolidine (stronger donor) accelerated ring-opening; this was also the case when a second donor function was introduced at C(1)



SCHEME 11



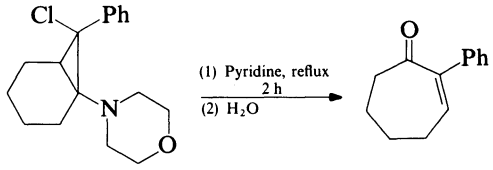
a: R = H
b: R = Ph



of **440** (e.g. X = OH[198–200, 206, 449], OER_n[205, 206], SH[446], carbon acid [381, 382, 453–456], 2-hydroxyphenyl[528]). The strongest effect was observed by interconversion of the amino into a metal-amino group (e.g. by $LiAlH_4$[457, 461–464, 474] or by RLi[529, 530]); in this case, ring-opening was already achieved at low temperatures[529]; the corresponding magnesium compounds seemed to be more stable[495, 517]. Cleavage of the cyclopropane ring, activated by an acceptor group in the 2-position, upon decarboxylation of a carbaminate also

demonstrates the influence of an anion character of the amino moiety (see Section II.A.1, equations 4–6 and the synthesis of piperidine-[281i, g] and indoline-lactones[428a, e]). A very fast ring-opening at −138°C was reported for aminyl radical c-C_3H_5-$\dot{N}R$[531]. Cycloaddition of halocarbenes onto enamines, especially onto pyrrolidinoalkenes, often led to products of a ring enlargement (**130**), which may be classified as a disrotatory ring-opening (see equation 32) or a homoenamine reaction[227, 228, 230–236, 244].

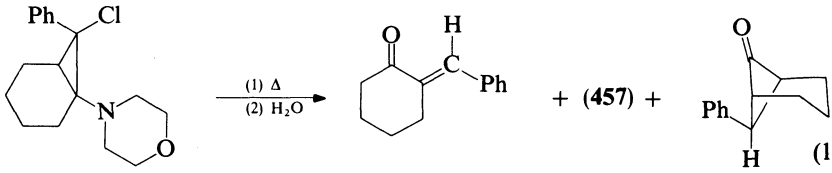
This was demonstrated by the diastereomeric compounds **456** and **458**. **456** gave **457** upon heating in pyridine and hydrolysis (equation 113); **458** was stable under these



(113)

(456) **(457)**

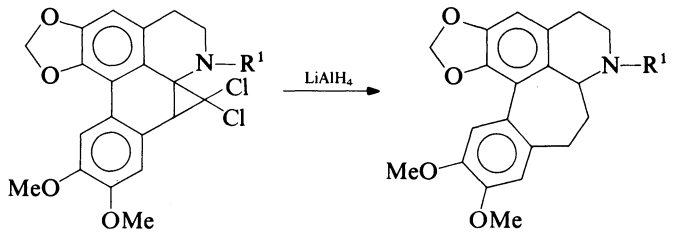
conditions, stronger heating of **458** however led to a mixture of **457**, **459** and **460**[232] (equation 114). The differences were discussed in terms of an electrocyclic process (**456** → **457**) on the one hand and a homoenamine reaction (**458** → **459** and **460**) on the other



(114)

(458) **(459)** 70% 20% **(460)** 10%

hand[232]. Ring enlargements by chloride displacement or by photolytic cleavage were used in the synthesis of cycloheptenone-[227, 231, 233–236, 239], azepine-[129, 252f–i, 283a, b] and 1,3-diazepine[252s, 281m, 282, 531a, b] derivatives or a homoaporphine (**461**)[247] (equation 115).

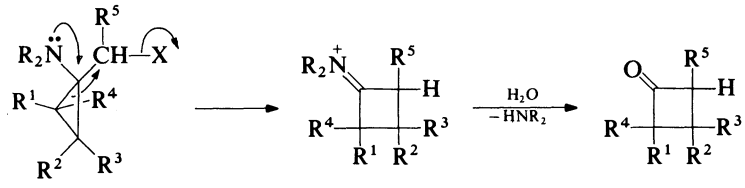


(115)

(138) R^1 = COOEt **(461)**

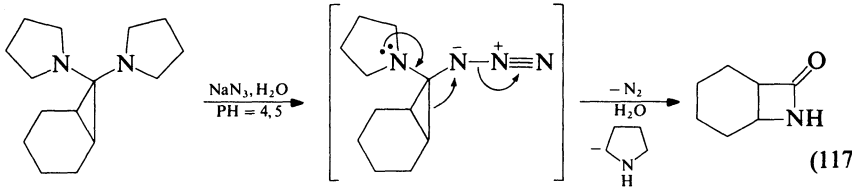
An electron-deficient center attached to an amino cyclopropane derivative generally causes a ring enlargement. Reactions of this type are shown in equations 116–119.

A carbon–carbon, carbon–nitrogen or nitrogen–nitrogen double bond in an aminocyclopropane allowed more or less easy homoenamine reactions (see also Section III.A.3.c



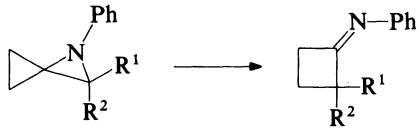
(462) (463) (464) (116)

$X = NH_2 \longrightarrow N_2^+$ [442, 532]
OH [481]
$^+SMe_2$ [533]



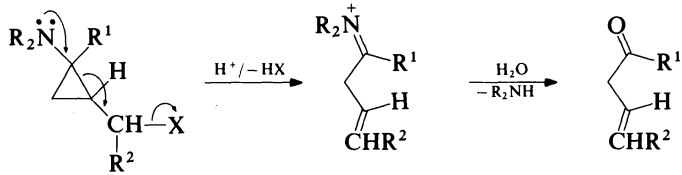
(465) (466) (467) (117)

Ref. 445



(468) (469) (118)

Refs. 209–211
see also Ref. 212

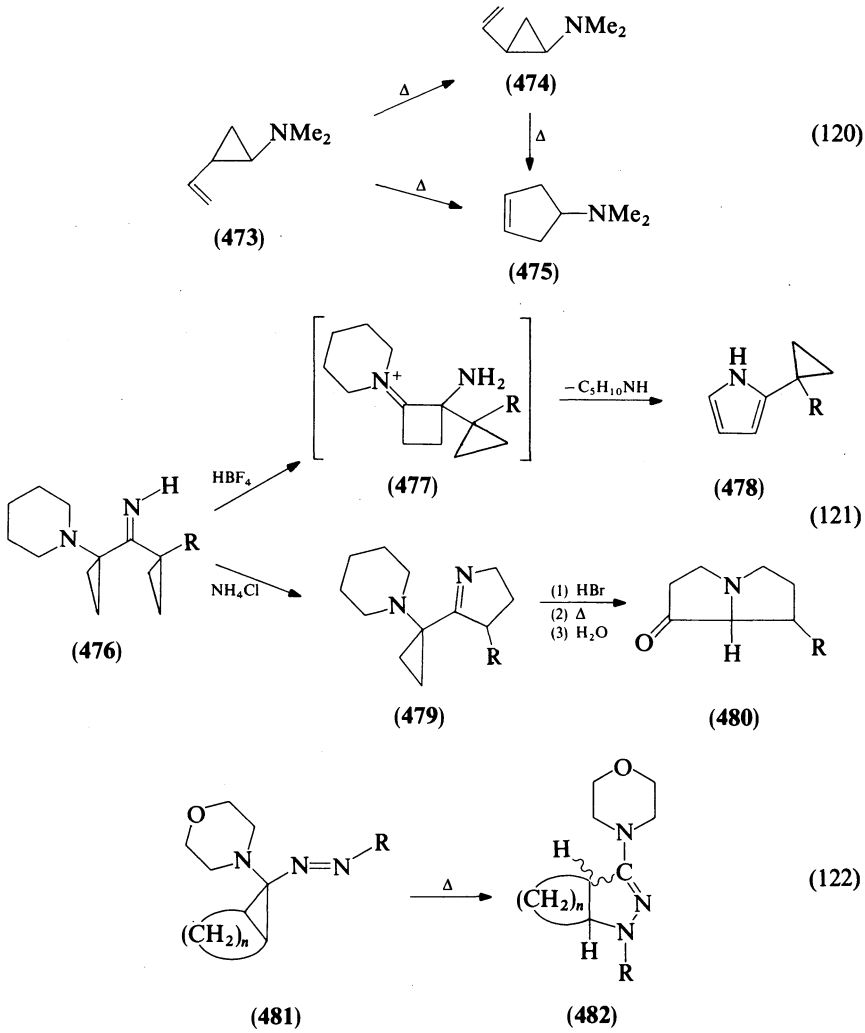


(470) (471) (472) (119)

e.g. $X = OR'$ [248]

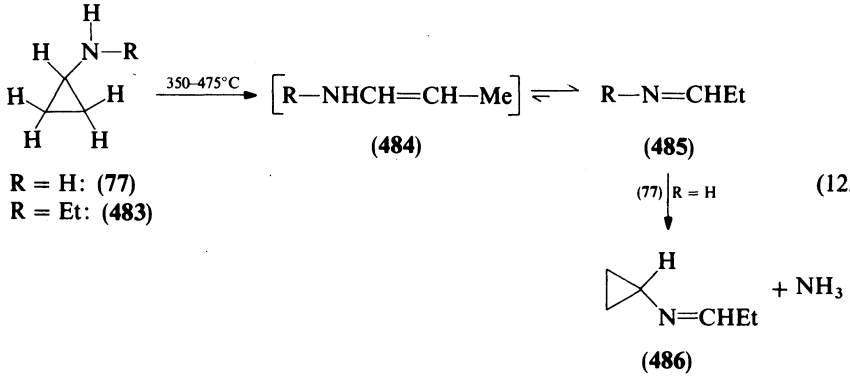
and III.A.3.d). Thus compounds **473** or **474**[534], **476**[450, 535], **479**[450, 535] and **481**[373] gave ring enlargement products **475**, **478**, **480** and **482**, respectively, upon heating (equations 120, 121 and 122).

Substituent effects on the ring-opening reaction have been observed upon thermolysis of aminocyclopropanes (**476**) (equation 121). Compounds **478**, which are derived from a homoenamine reaction, have been the only isolated products from heating **476** in the presence of HBF_4[535]. On the contrary, NH_4Cl as a catalyst caused the ring-opening of the



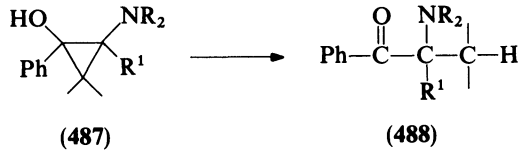
cyclopropane ring which did not carry the amino substituent. The formation of **479** and **480** was explained by an attack of the halide on the three-membered ring and a subsequent ring-closure involving the imino nitrogen[450, 535].

Unsubstituted cyclopropylamine (**77**) gave a mixture of **486** and ammonia upon thermolysis[536–538] (equation 123). **486** is formed from the product of a homoenamine reaction **485** and excess **77**. Intermediate **484** (R = H) was observed by the IR spectrum in the gas phase[539]. The reaction **485** → **486** did not take place with ethylaminocyclopropane (**483**); in this case **485** (R = Et) could be isolated[536]. Insertion of carbon monoxide into the vicinal carbon–carbon bond of **77** in the presence of rhodium catalysts produced γ-lactams[540]. Thermolysis of a homoazepine led to a vinyl dihydropyridine[540a], heating of a homopyrrole or bishomopyrrole gave products derived from an azomethine ylide intermediate[281a, b, 540b–d].



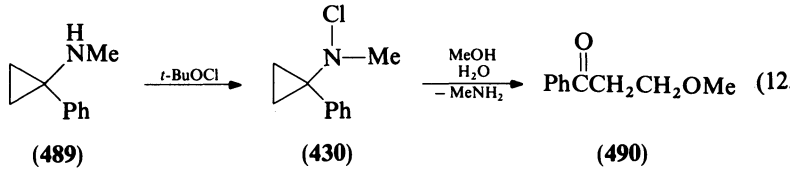
(123)

Compounds **488** have been obtained from cyclopropanes **487** containing both a hydroxy and an amino moiety[420–422] (equation 124). Consequently, **487** behave more as a homoenol or homoenolate than as a homoenamine.



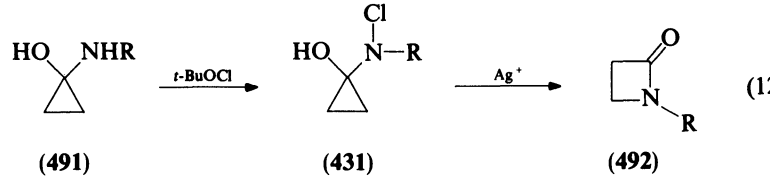
(124)

Opening of the vicinal carbon–carbon bond in aminocyclopropane derivatives was achieved by oxidation with various reagents, e.g. $Pb(OAc)_4$[541–543], $NaOCl$[511, 541, 543], *t*-BuOCl[510], Cu^{2+}/O_2[544], Cu/O_2[545], OsO_4/O_2[545] $K_3Fe(CN)_6$[546], Cu^{2+} or Fe^{3+}[204], $h\nu/O_2$/sens.[547], anodic oxidation[546, 548]. Oxidation with halogenating reagents such as NaOCl or *t*-BuOCl proceeds via *N*-chloro compounds (see equation 105), which opened the C(1)–C(2) cyclopropane bond when the cyclopropylamine had one substituent at the *N*-atom (e.g. **489** → **490**[510, 511], equation 125) or a phenyl moiety in the C(2) position.



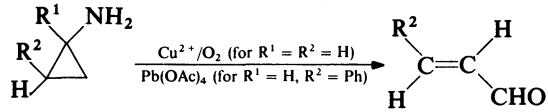
(125)

Ring-opening after *N*-chlorination of 1-hydroxycyclopropylamines (**491**) was used in the synthesis of β-lactams (equation 126)[194, 196, 197, 219, 447]. *N*-Unsubstituted-1-substituted cyclopropylamines are cleaved in a cycloelimination reaction by chlorinating or other



(126)

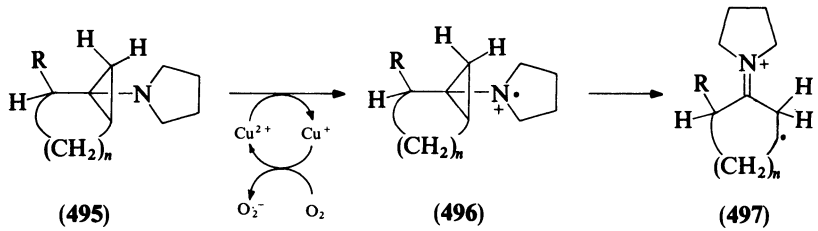
oxidizing reagents (see Section III.A.5). $Pb(OAc)_4$ reacted with aminocyclopropanes also in different ways depending on the substituents in **493**. Compounds **493** in which R^1 is a hydrogen atom gave acrolein derivatives (**494**)[541, 543] (equation 127). A 2-hydroxycyclopropylamine was transformed into a 1,3-dione by the same reagent[542].



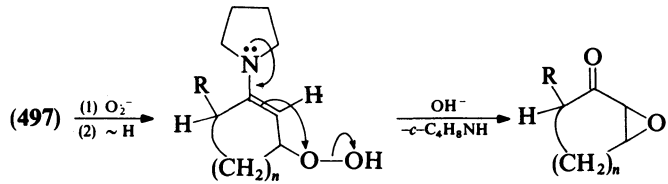
(127)

(493) (494)

A less common type of oxidative ring-opening of aminobicyclo [n.1.0]alkanes (**495**) is shown in Scheme 12; here, epoxyketones (**499**) are obtained by oxidation with Cu^{2+}/O_2. The unexpected formation of **499** could result from the intermediacy of **496–498**[544], but other pathways are also feasible.



(495) (496) (497)



(498) (499)

SCHEME 12

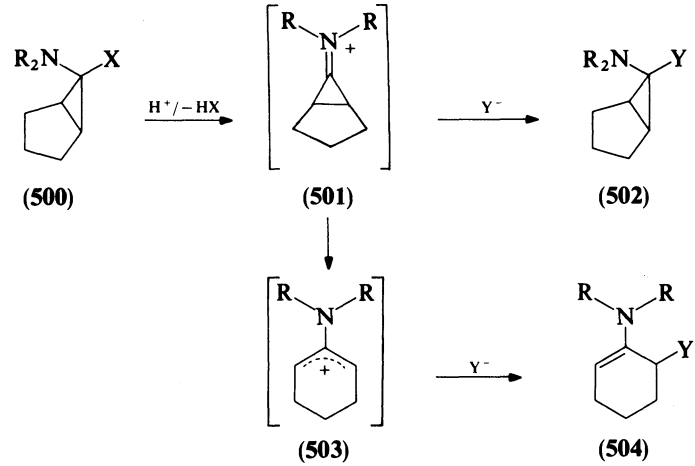
b. Opening of the distal cyclopropane C(2)–C(3) bond

Ring-opening reactions of the distal bond of aminocyclopropanes are of minor importance. Sometimes this type of reaction is observed in nucleophilic substitution of aminobicyclo[3.1.0]hexane derivatives (**500**) leading to **504** instead of **502**[342,370,443,444] (equation 128). The ring-opening tendency is a consequence of the lower stability of **501** with respect to other cyclopropaniminium ions[443].

For further reactions with opening of the distal carbon–carbon bond in an aminocyclopropane see Sections III.A.3.c and III.A.3.d and Ref. 427.

c. Hydrogenolysis

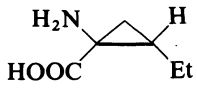
In general the less stable bond of a cyclopropane ring is cleaved by a hydrogenolysis reaction, e.g. Ref. 549. In aminocyclopropane derivatives the C(2)–C(3) bond proved to be



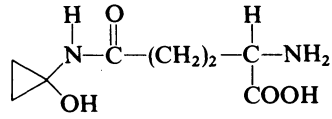
longer than the C(1)–C(2) or the C(1)–C(3) bond, but the differences between the distances are small (as shown by X-ray structure analyses[297, 339, 342, 349, 373, 374, 414, 502, 550–557], microwave spectra[558–560], MO calculations[492, 561–565]).

Thus hydrogenolysis of coronamic acid (**505**) led to a mixture of isoleucine, alloisoleucine, norleucine and 2-amino-2-methylvaleric acid[555, 566]; this demonstrates, that all three bonds of the cyclopropane ring are cleaved and this reaction was used for the assignment of configuration of optically active **505**[555, 566]. Exclusive opening of the cyclopropane C(2)–C(3) bond was reported for hydrogenation of coprine (**506**)[416] or a bicyclo[3.1.0]hexanone aminal[58].

Hydrogenolytic cleavage of the cyclopropane C(1)–C(2) bond was observed in a spirooxazolone (**165**)[295] (for an X-ray structure analysis of a compound **165** see Ref. 291).



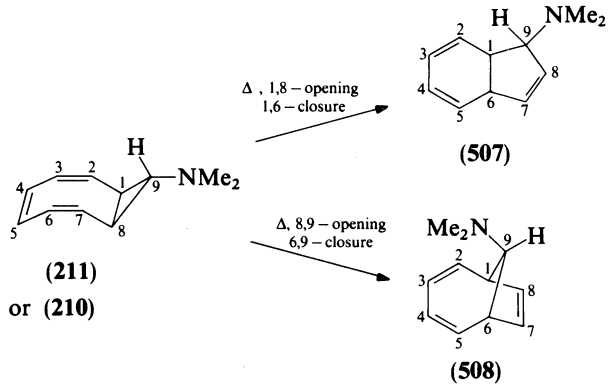
(**505**)



(**506**)

d. Electrocyclic ring-opening

Electrocyclic ring-opening reactions have been observed for the cycloheptatriene/norcaradiene system **316** ⇌ **317**[462] (see equation 74). 9-aza-barbaralane[408a–c], a 6-azabenz[10]annulene system[188e], α-methylaminobicyclo[6.1.0]nonatriene (**210**/**211**) leading to **507** and **508**[328] (equation 129) and azaquadricyclan (**364**) generating **509**[438a, d, e] (equation 130). An electrocyclic process, in which two imino groups were involved, was found in the reaction of 1,2-diaminocyclopropanes with aldehydes[49, 133, 279, 504–509]. *Cis*-1,2-bisimines (**425**), especially, underwent a very fast Cope rearrangement, yielding diazepines (**510**) (equation 131). The formation of **510** from the *trans*-1,2-bisimines (**424**) required heating to 90–160°C or sodium acetate/methanol catalysis (20–25°C)[504–506, 508, 509]. Both *cis*- and *trans*-1,2-bis(alkylamino)cyclopropanes (**511**) reacted with aldehydes to give pyrroles (**514**)[133, 509] (equation 132). In this case, ring enlargement of an iminium cation (**512**) seemed to be more favorable than the Cope rearrangement of a bisiminium dication[508, 509].

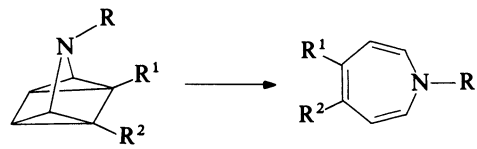


(211)
or (210)

(507)

(508)

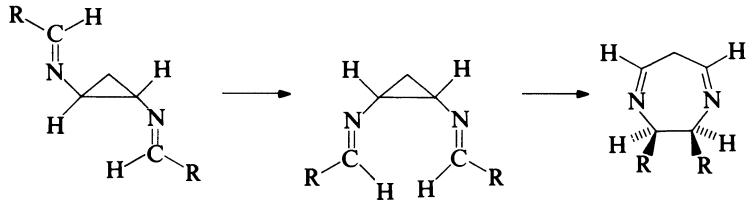
(129)



(364)

(509)

(130)

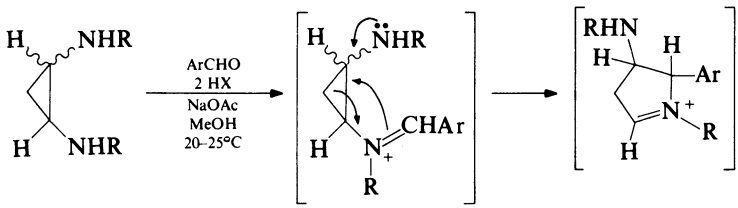


(424)

(425)

(510)

(131)

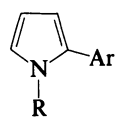


(511)

(512)

(513)

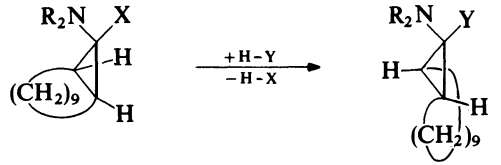
(132)



(514)

4. *Isomerization reactions*

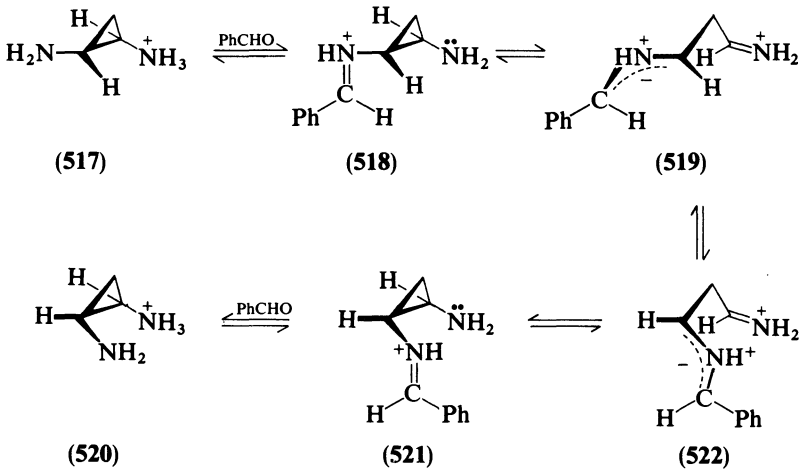
Change of configuration around the C(2)–C(3) bond was found in some nucleophilic substitution reactions of aminobicyclo[9.1.0]dodecane derivatives (**515**)[359,456] (equation 133). The isomerization was assumed to take place at the stage of an aminoally cation, which is in equilibrium with a bicyclic iminium ion (see also equations 95 and 96).



(515) (516) (133)

Formation of 1,2-bisimines **424** or **425** from diaminocyclopropanes **517** and **520** and aldehydes in acetate-buffered methanol resulted in a *cis–trans* isomerization at room temperature (for isomerization of a *cis*-1,2-diaminocyclopropane see Ref. 279). A detailed study pointed out that isomerization is best described as involving the intermediates **518**, **519**, **521** and **522**[279,508,509] (Scheme 13).

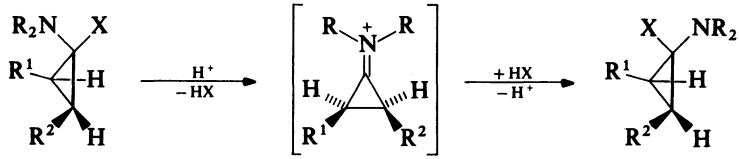
Change of configuration around the C(1)–C(2) or the C(1)–C(3) bond does not necessarily afford a ring-opened species as an intermediate. Conversion of **523** into **525** occurred via iminium ion (**524**), which is attacked by the nucleophile from the more hindered position forming the thermodynamically more stable product (equation 134) For *endo–exo* isomerization, see equation 91). Isomerization of **523** (R^1 = Ph, R^2 = H, X = CN) was discussed in terms of a diradical intermediate stabilized by the 'capto-dative' substituent combination[567].



(517) (518) (519)

(520) (521) (522)

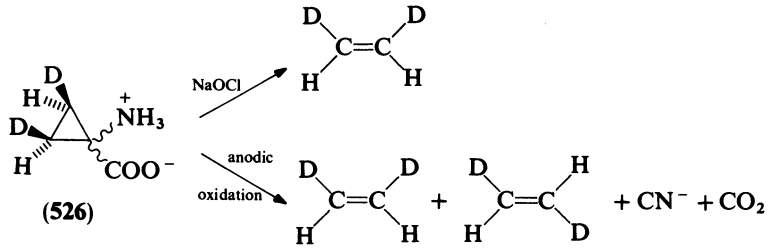
SCHEME 13



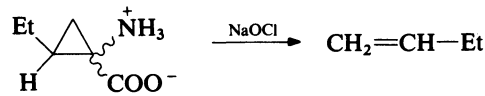
(523) (524) (525) (134)

5. Cyclopropane cleavage by cycloelimination

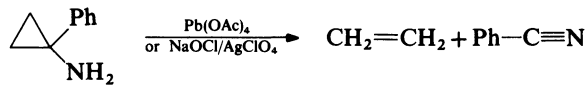
Alkene formation by cycloelimination has also been observed for several aminocyclopropane derivatives. Thus amino acids **526** (equation 135) and **527** (equation 136) were converted into ethene and 1-butene, respectively by electrochemical oxidation[320] or interaction with other oxidizing reagents, e.g. NaOCl[326, 568, 569], aqueous chromic acid[4], hydroxyl radicals[570], $CuSO_4$[571], $KMnO_4$[571] or K_2FeO_4[571]. The *cis* relationship of the deuterium atoms in **526** remained unchanged in the conversion to ethene by NaOCl[326] but not upon anodic, $CuSO_4$, $KMnO_4$ or K_2FeO_4 oxidation[326, 571]. These stereochemical differences are explained by the participation of either a nitrene or a cation radical intermediate[571]. In the case of **434**, $Pb(OAc)_4$ was reported to be better suitable for the oxidation than NaOCl[541, 543] (equation 137) (for reaction of 1-unsubstituted aminocyclopropanes with $Pb(OAc)_4$ see Section III.A.3.a, equation 127).



(526) (135)

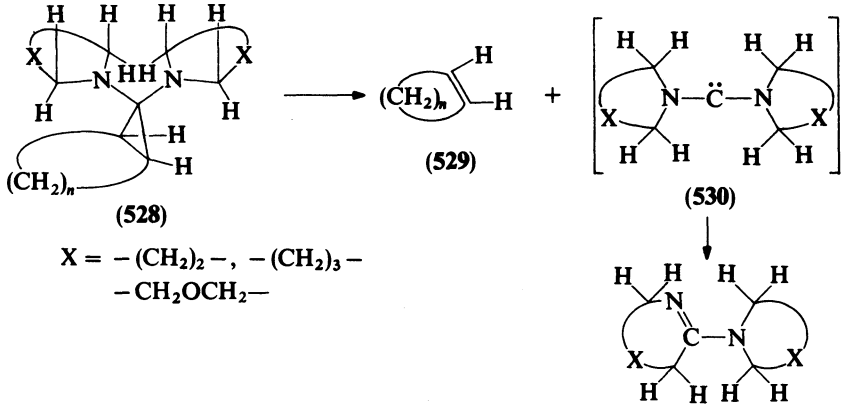


(527) (136)



(434) (137)

Diaminocyclopropane derivatives (**528**) were cleaved upon vacuum flash pyrolysis. Besides cycloalkene (**529**), amidines (**531**) were obtained in 76–91 % yield. Compounds **531** were believed to be the result of a ring enlargement of the initially formed diaminocarbenes (**530**) (equation 138). Pyrolysis of *cis*- and *trans*-bicyclododecane derivatives occurred with distinct stereoselectivity during cycloelimination[572] (ratio of *cis*-: *trans*-cycloundecene: 93 : 7 and 13 : 87 respectively).



(528) (529) (530) (531)

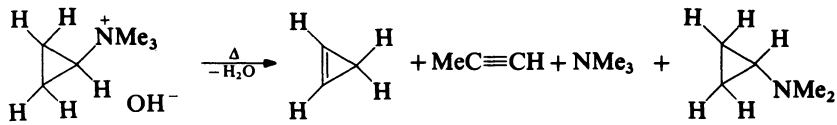
X = $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH_2OCH_2-$

(138)

6. Removal of the amino function

a. By formation of cyclopropenes

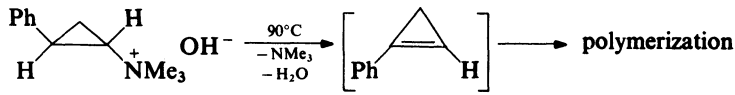
Cyclopropene (**533**) has been prepared by Hofmann elimination of the quaternary ammonium salt (**532**)[10, 12, 180, 573] (equation 139). Decomposition of **532** at 90–100°C was reported[573] to give better results than thermolysis at 320–360°C in the presence of kaoline[10] or platinized asbestos[12] as a catalyst. By the latter method, **534** was obtained as well as **533** by attack of an hydroxide on the *N*-methyl group of **532**.



(532) (533) (534)

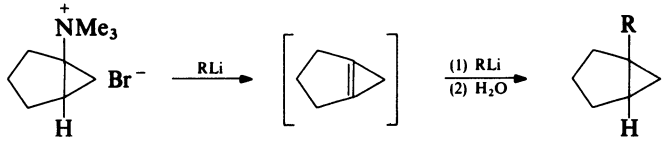
(139)

An optically active diethylcyclopropene was prepared from the corresponding optically active trimethylcyclopropylammonium salt[92]; cyclopropene (**536**) could not be prepared by pyrolysis of phenylcyclopropylammonium hydroxide (**535**); the volatile product polymerized at $-70°C$[169] (equation 140). A difunctional cyclopropenylcyclopropene was not accessible by a twofold Hofmann elimination[80]. Elimination of the amino group of **537** could be achieved by lithium organyls (equation 141). In this case, the highly reactive cyclopropene (**538**) took up further lithium organyl, forming **539** after hydrolysis[266]. A benzylcyclopropyldimethylammonium salt gave cyclopropene (**533**) only to a minor



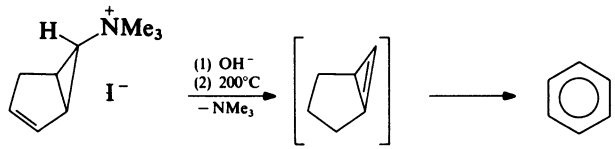
(535) (536)

(140)



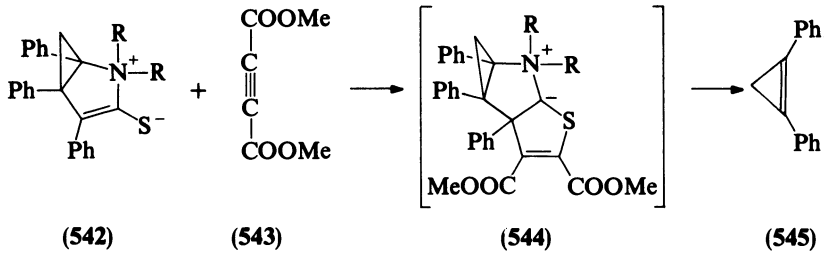
(537) (538) (539) (141)

extent upon addition of $NaNH_2$[477]; the main product resulted from a Sommelet–Hauser rearrangement. Bicyclic cyclopropene (**541**) was postulated as an intermediate in the pyrolysis of bicyclic ammonium salt **540** leading to benzene and trimethylamine[168] (equation 142).

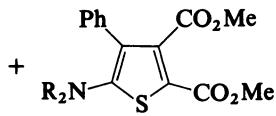


(540) (541) (142)

Cyclopropene (**545**) and thiophene (**546**) were isolated from the reaction of betaine (**542**) with dimethyl acetylenedicarboxylate (**543**) (equation 143). This reaction is understood quite well by the formation and decomposition of intermediate **544**[334, 340].



(542) (543) (544) (545)



(546)

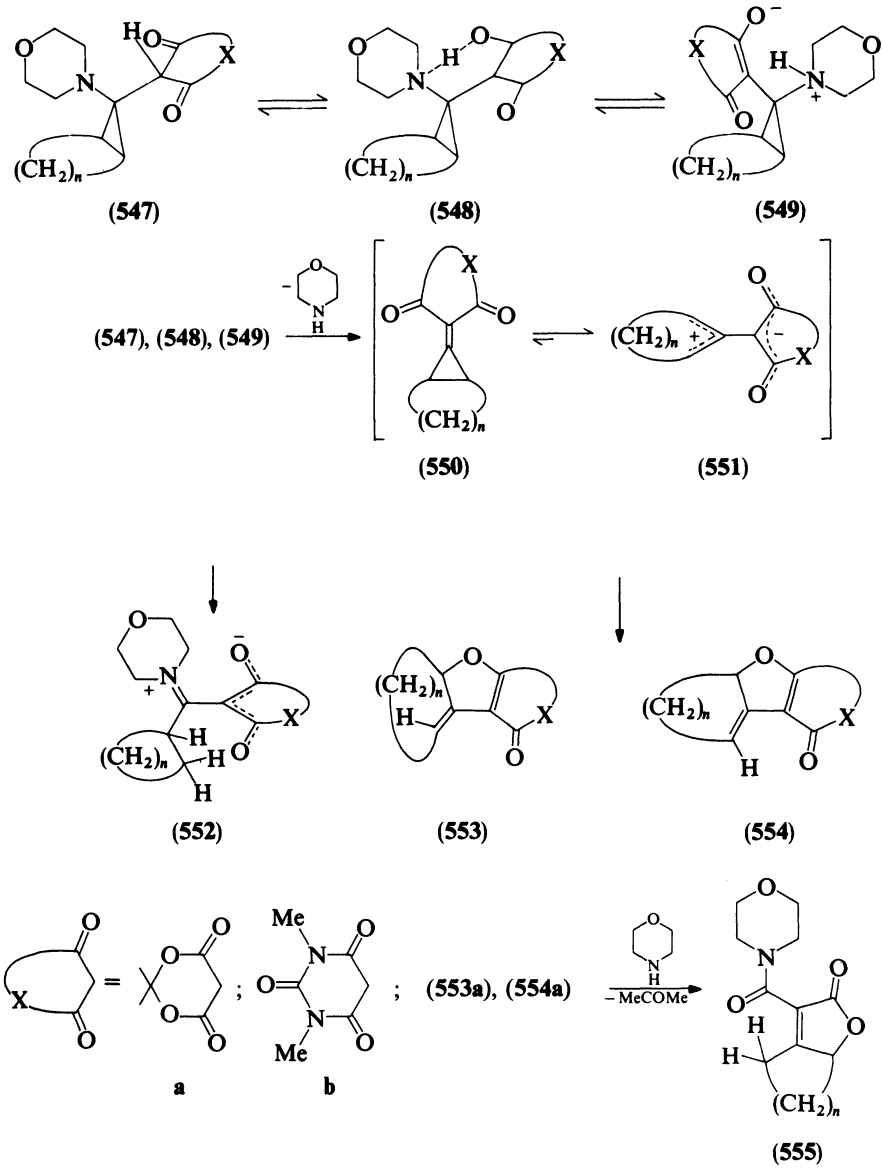
(143)

A cyclopropene (**533**) could not be isolated from the pyrolysis of cyclopropyldimethylamine oxide[180].

b. Via formation of a methylenecyclopropane intermediate

Aminocyclopropane derivatives possessing an acidifying substituent on carbon proved to be useful for the generation of methylenecyclopropane intermediates (**550**), which are

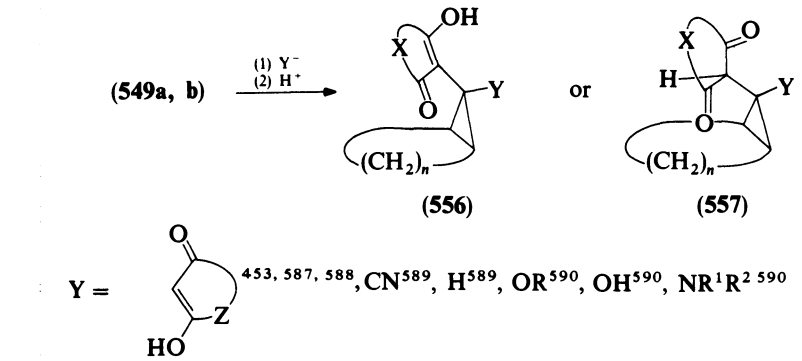
the starting point for further reactions. Heating of compounds **547**, **548** or **549** led to derivatives **553**, **554** or **552**[381, 382, 452–455]. The former products are derived from a methylenecyclopropane intermediate (**550**), the latter result from a homoenamine reaction (Scheme 14) (see also Section III.A.3.a). The course of the reaction depended on the ring size, the carbon acid and the amino function in **547**, **548** or **549**. Generally, the



SCHEME 14

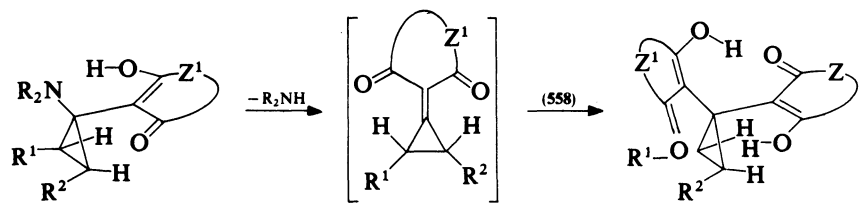
bicyclo[3.1.0]hexane and bicyclo[9.1.0]dodecane system formed methylenedihydrofurans **553** and **554**, respectively. Bicyclo[4.1.0]heptane or bicyclo[5.1.0]octane derivatives gave either **552** or **554**. Decreasing acidity of the 1,3-dicarbonyl group favored homoenamine ring-opening. Meldrum's acid, a relatively strong carbon acid, afforded amine elimination in every case, but here a subsequent reaction of **553** or **554** with morpholine yielded compounds **555**[382].

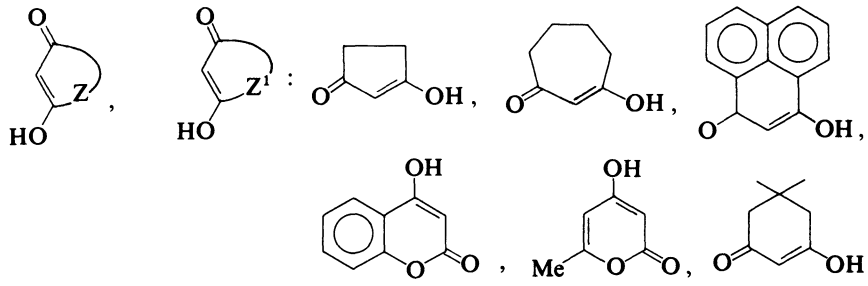
Methylenecyclopropanes with two acceptor substituents are very unstable[574-585] (exceptions are reported in Refs. 575, 580, 586). They undergo an easy ring-opening to a zwitterion (**551**), which forms dihydrofurans **553** or **554**. In some cases intermediates **550** could also be trapped by nucleophiles without opening of the three-membered ring; alltogether this reaction effects a displacement of the amino moiety by a nucleophile (equation 144). Thus morpholine could be substituted in compounds **549a,b** bearing a barbituric acid or Meldrum's acid moiety by various nucleophiles leading to **556** or **557**[453, 587-590]. Thus, *exo*-morpholino derivatives **549** were necessary as starting materials.



(**558**) for Z see equation 145 (144)

Other bicyclic compounds (**559a**) with a 1,3-dicarbonyl group in the *exo*-position, thus far could only be transformed into symmetrically substituted products[454,591] (**561a** $Z = Z^1$) (equation 145). Interestingly, trapping of **560a** in these latter cases was only successful with the bicyclooctane and partially bicycloheptane system. These are the ring sizes which gave homoenamine products upon thermolysis. In monocyclic compounds (**559b**) steric discrimination disappears and consequently in all cases compounds **561** with both identical ($Z = Z^1$) and different ($Z \neq Z^1$) substituents could be synthesized[455].



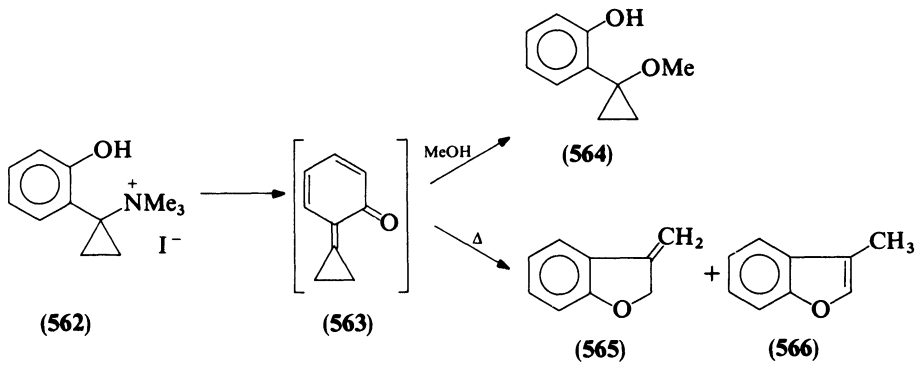


(559)–(561)

a: $R^1, R^2 = -(CH_2)_5-, Z = Z^1$

b $R^1 = R^2 = H$ (145)

Heating of ammonium salt (**562**) generated intermediate **563**, which could be trapped by methanol leading to substitution product **564**[528, 592]. Thermolysis of **562** in the absence of a trapping reagent gave a mixture of **565** and **566** in a low yield[528, 592] (equation 146). Pyrolysis of compound **562** with a dimethylamino moiety instead of the trimethylammonium group caused a homoenamine reaction rather than amine elimination[528].



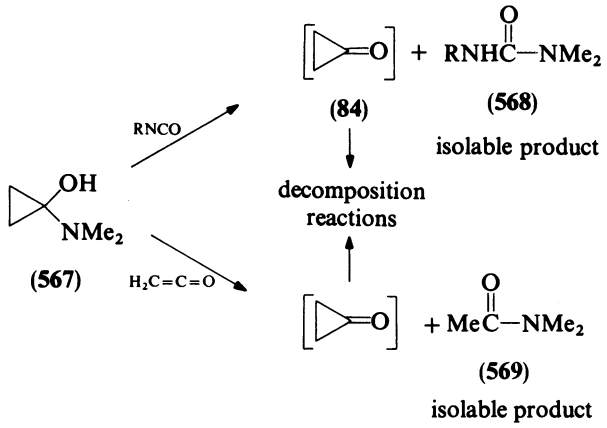
(562) (563) (564) (565) (566)

(146)

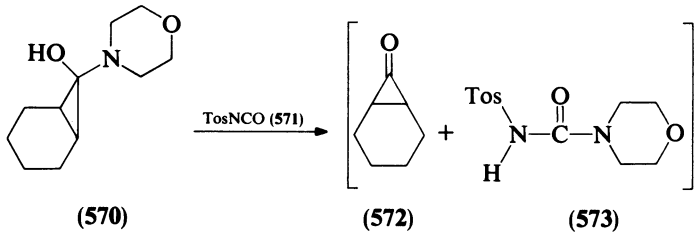
c. Via formation of a cyclopropanone

Semiaminal (**567**) reacted with nucleophiles generally by a replacement of the hydroxy group[195, 198, 199, 204, 400, 449–452]. Only few exceptions were known. For example, reaction of **567** with ketene or isocyanates caused acylation and displacement of the secondary amino moiety[449] (equation 147); cyclopropanone (**84**) could be detected spectroscopically in one case[449]. A similar removal of the amino function by tosyl isocyanate (**571**) was observed with **570**[593], but here compound **574** was isolated in 47% yield (equation 148). **574** resulted from a subsequent addition of the initially formed products **572** and **573**[593]. Steric reasons led to the sequence **570** → **574**; the diastereomeric *endo*-morpholino semiaminal reacted with **571** by displacement of the *exo*-hydroxy group.

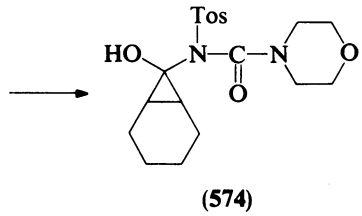
Steric reasons may also be responsible for substitution of the *exo*-pyrrolidino moiety in **575** by H^- [342, 343] or, after quaternization, by MeO^- [445] leading to **576** and **577**, respectively (equation 149).

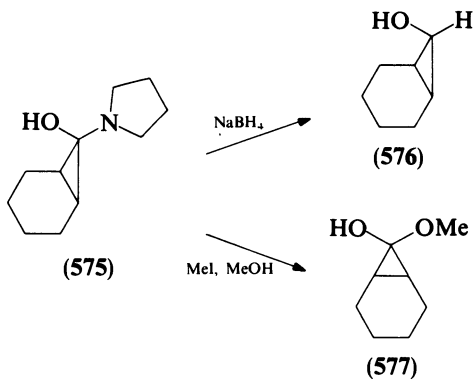

RNCO
OH
NMe2
(567)
H2C=C=O
(84)
+ RNHC(=O)NMe2
(568)
isolable product
decomposition reactions
+ MeC(=O)NMe2
(569)
isolable product

(147)


HO
N
O
TosNCO (571)
Tos
(570)
(572)
(573)

(148)

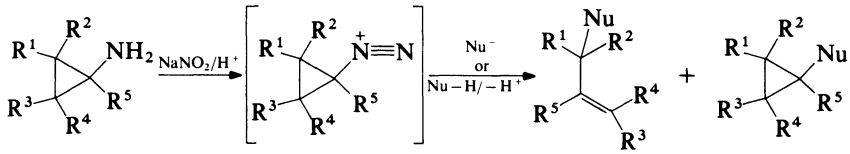

Tos
HO
N
C
O
(574)


HO
N
(575)
NaBH4
HO
H
(576)
MeI, MeOH
HO
OMe
(577)

(149)

d. Via formation of a cyclopropyldiazonium, a diazocyclopropane or a cyclopropyldiazene intermediate

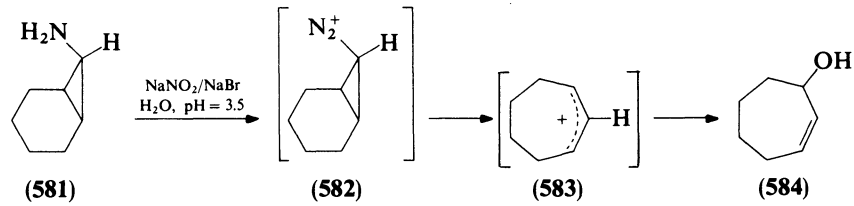
A primary amino function in aminocyclopropanes (**413**) can be removed easily by diazotation (for a review see Ref. 594). In the absence of any steric restrictions, displacement of the diazonium group led mainly to ring-opened allylic substitution products (**579**)[3, 4, 11, 53, 84, 86, 144, 147, 595] (equation 150). Substituted cyclopropanes (**580**) are obtained only to a very small amount; they were formed mainly (> 92%) with inversion of configuration[147] (see also Ref. 218).



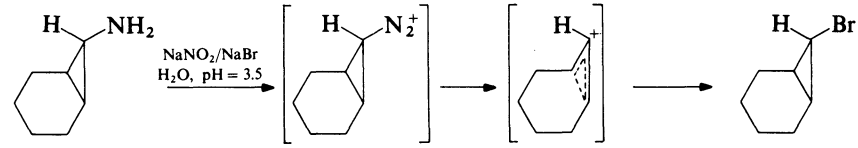
(413) (578) (579) (580)

(150)

On the other hand the amino moiety in some bi- or polycyclic aminocyclopropanes could be substituted by diazotation without appreciable ring-opening[23, 56, 61, 110, 124, 147, 152]. The great steric influence of the diazonium group on the substitution was pointed out by Kirmse and Jendralla[110] upon using the diastereomeric amines **581** and **585** (Scheme 15). Allylic alcohol (**584**) was obtained as the main product from diazotation of **581**. The same procedure with the *exo*-amine (**585**) furnished mainly **588** besides a small amount of **584**. The small crossover of the reaction paths was partially caused by *exo–endo* isomerization of the diazonium species **582** and **586**. This demonstrates clearly that removal of the diazonium function is accompanied by a ring-opening in the bicyclic series. By Woodward–Hoffmann allowed electrocyclic ring-



(581) (582) (583) (584)



(585) (586) (587) (588)

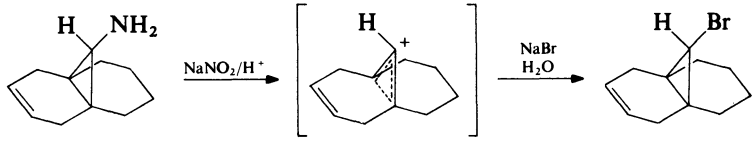
(581) ⟶ 94.0% (**584**) + 4.2% (**588**) (total yield, 85%)

(585) ⟶ 5.0% (**584**) + 92.5% (**588**) (total yield, 63%)

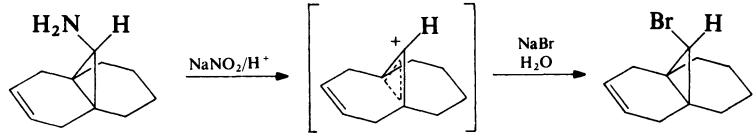
SCHEME 15

opening, **582** generated a *cis*-cycloheptenyl cation (**583**), whereas, due to steric strain, from the *exo*-diazonium ion **586**, only a 'half-opened' cyclopropyl cation[596–600] (**587**) is formed, leading to substitution product **588**. For earlier reports on diazotation of **585** see Refs 45, 47, 601; for the formation of a *cis–trans*-cycloheptadienylium species see equation 158[602].

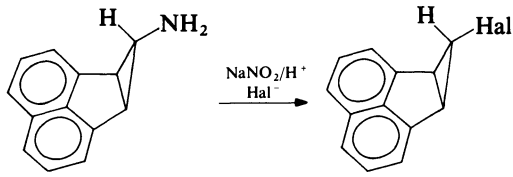
Similar steric restrictions of a ring-opening gave substitution products **591**, **594**, **596**, **598** and **600** from the diazotation of amines **589**, **592**[147], **595**[56, 61, 62, 124], **597**[23] and **599**[152] in the presence of a high concentration of nucleophile (equations 151–155). Substitution of the amino moiety in **589** and **592** proceeded with 97–99% retention of configuration as a consequence of a participation of 'half-opened' cyclopropyl cationic species[596–600] **590** and **593** in the substitution process[147] (equations 151 and 152).



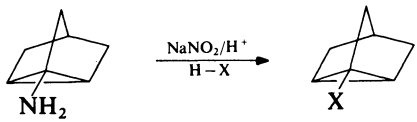
(589) (590) (591) (151)



(592) (593) (594) (152)

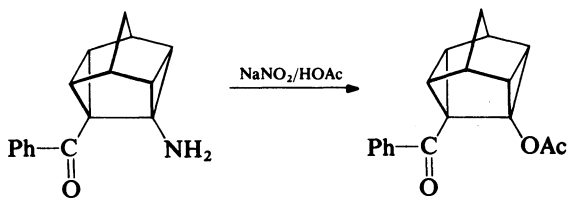


(595) (596) (153)



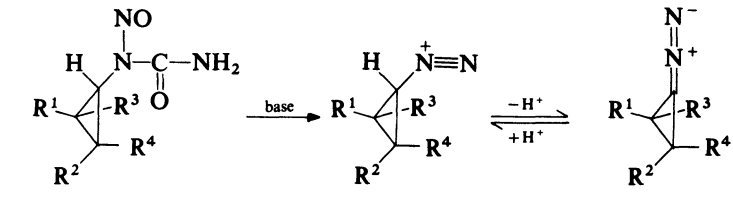
(597) (598) (154)

X = OH, OAc

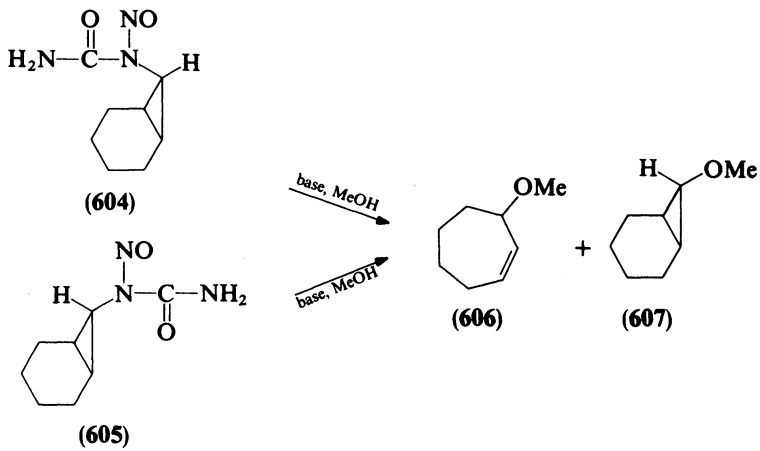


(599) (600) (155)

Cyclopropyldiazonium species **602** could also be generated from *N*-cyclopropyl-*N*-nitrosoureas (**601**) by deprotonation[25, 28, 69, 74, 83, 96, 97, 99, 107–110, 115, 120, 121, 127, 137–139, 141, 173, 174, 602–605] or by decomposition in methanol with $CuSO_4$ as a catalyst (e.g. Ref. 110) (equation 156). It has already been demonstrated with bicyclic species, that *exo–endo* isomerization took place in neutral or weakly alkaline medium[74, 96, 97]. It has been shown by diazotation of bicyclic amines such as **581** and **585** that the diazonium group was more easily replaced from the *exo*-position of a bicyclo[4.1.0]heptane[110] or bicyclo[5.1.0]octane[74] system than from its *endo*-position. A contrary behavior was found for bicyclo[3.1.0]hexane compounds[74]. Nitrosoureas **604** and **605** gave an identical mixture of **606** and **607** upon addition of $NaHCO_3$, HCOONa or Na_2CO_3 in methanol[28, 110] (equation 157). Isomerization took place via a diazocyclopropane (**603**) intermediate as indicated by deuterium incorporation from MeOD.



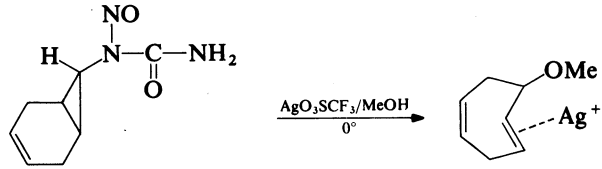
(601) (602) (603) (156)



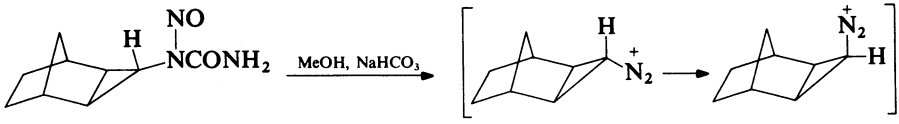
(604) (606) (607)

(605) (157)

In other cases isomerization was not much faster than dinitrogen elimination in spite of the use of nitrosoureas as starting materials. Thus a silver ion stabilized *cis–trans* cycloheptadiene derivative (**609**) could be obtained from *exo*-nitrosourea. (**608**) and CF_3SO_3Ag in methanol[602] (equation 158). Steric influences on the isomerization reaction and therefore on the decomposition path of diazonium ions were demonstrated by cleavage of the nitrosoureas **610** and **614** in weakly alkaline medium[97]. Diazonium ion **611** isomerized quickly to **612** producing only products from a ring-opening reaction (equation 159). In contrast, deprotonation and isomerization rates are slower for **615**, which therefore gave **617** (via a 'half-opened' cyclopropyl cation) as well as ring-opened products derived from **616**[97] (equation 160). Isomerization reactions are excluded in a bicyclic nitrosourea bearing an α-methyl group[120].

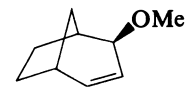


(608) (609) (158)



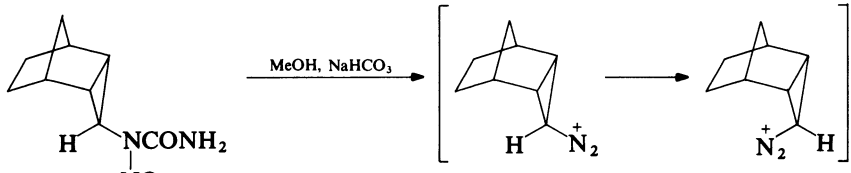
(610) (611) (612)

only products of ring opening

e.g. 

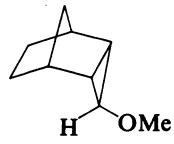
(613)

(159)



(614) (615) (616)

products of ring opening

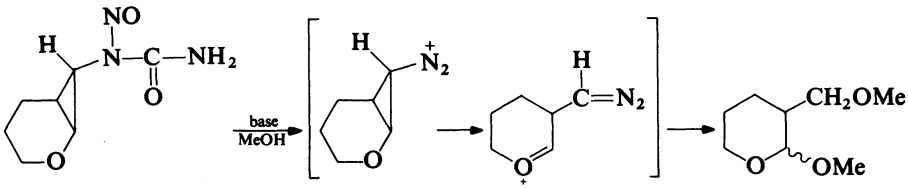


(617) e.g. (613)

35% 65%

(160)

Generation of a diazonium intermediate (**619**) from nitrosourea (**618**) gave products, which are derived from intermediate **620**[121] (equation 161). Surprisingly, in this special case the C(1)–C(2)-bond of the cyclopropane was cleaved. In contrast, diazonium species of a 3-oxa-bicyclo[4.1.0]heptyl or 3,5-dioxabicyclo[5.1.0]octyl system decomposed via an



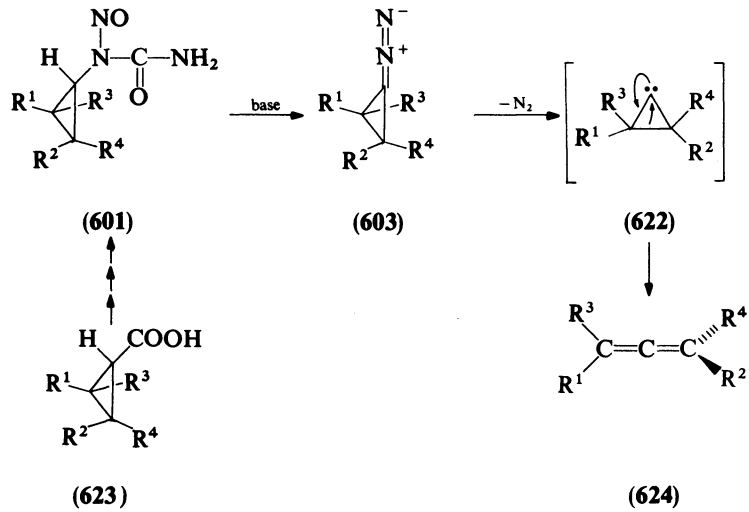
(618) (619) (620) (621)

and other products

(161)

opening of the C(2)–C(3) bond of the cyclopropane[136, 137], in analogy to the alicyclic systems.

Interaction of a strong base with nitrosoureas **601** led to the formation of diazocyclopropanes **603**, which proved to be less stable and to decompose via a carbene intermediate (**622**) (for trapping of **603**, see Refs 43, 101, 174, 606), rearranging to allenes (**624**)[39, 43, 44, 50, 68, 74, 83–85, 88, 141, 174, 606, 607] (Scheme 16). Allene rearrangement was also reported for a cyclopropyl-1,2-bisnitrosourea[85]. By the sequence **623** → **624** allenes could be synthesized in good yields. It was shown that optical activity was transferred from the nitrosourea precursor **601** (central chirality) to the allene product **624** (axial chirality)[44, 50, 68, 88].

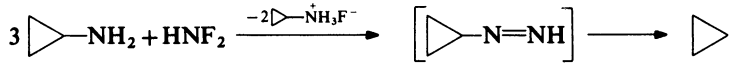


SCHEME 16

Alternatively inter- or intramolecular insertion or cycloaddition reactions have been observed, leading sometimes to a complex spectrum of products[28, 96, 107–110, 141] (for trapping of carbene **622** see Refs 39, 43, 605, 608, 609).

Cyclopropyl derivatives were obtained in addition to allylic derivatives from the reaction of *N*-cyclopropyl-*N*-nitrosoureas (**601**) with various nucleophiles, e.g. H^-[28, 74, 96] or

I^- [69]. N_3^- as a nucleophile gave mainly cyclopropyl azides to a greater extent[25, 28, 69, 115, 117, 138, 139, 604]. This is the consequence of an azo coupling leading to a pentazene and a pentazole intermediate as demonstrated by using 1-^{15}N- and 2-^{15}N-labeled nitrosourea[25, 28]. A secondary amine generated the triazene derivative in addition to a cyclopropane substitution product from **601**[25]. Cyclopropyl diazonium species **602** could also be trapped by a cycloaddition reaction[25]. A special reaction of a diazocyclopropane compound was found with a bicyclo[6.1.0]nonatriene system, which gave diazoindene by a electrocyclic ring-opening, followed by ring-closure[134]. A cyclopropyldiazene (**625**) was postulated as an intermediate in the deamination of cyclopropylamine (**77**) by difluoroamine, leading to cyclopropane (**403**) in 77% yield[610] (equation 162).



(77) (625) (403) (162)

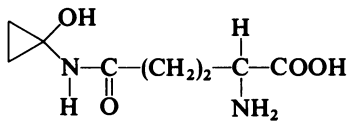
B. Biochemical Activities and Applications of Aminocyclopropanes

In 1971 Burger[611] reviewed biochemical activities of cyclopropane compounds; almost half of this review deals with aminocyclopropane derivatives. In 1975, a similar review on the same topic was published by Otto[612].

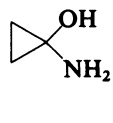
It is not intended to list here all aminocyclopropane compounds with pharmacological or biochemical effects nor to mention the numerous papers dealing with investigations of the most outstanding aminocyclopropane derivatives such as tranylcypromine (see Section III.B.2) or aminocyclopropane carboxylic acid (see Section III.B.3). Biochemical aspects of aminocyclopropane derivatives are part of Chapter 16, which gives more comprehensive information.

1. 1-Hydroxycyclopropylamines as inhibitors of acetaldehyde dehydrogenase

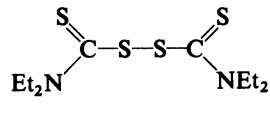
Coprine (**506**) was isolated from the inky cap mushroom *Coprinus atramentarius*[203, 204, 416, 613]. The mushroom proved to be non-toxic generally, but it caused severe illness when taken together with alcohol. It was found that semiaminal **4**, the product of hydrolysis of **506**, was the active substance inhibiting acetaldehyde dehydrogenase[203, 204, 416, 613–624]. Therefore, acetaldehyde as an oxidation product of ethanol is accumulated in the presence of **4** *in vitro* and *in vivo* or in the presence of **506** *in vivo*. **506** was more potent as an inhibitor



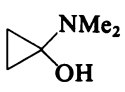
(506)



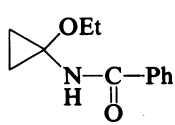
(4)



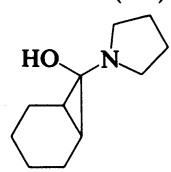
(626)



(567)



(627)



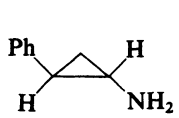
(575)

of acetaldehyde dehydrogenase than the well known disulfiram (**626**)[617]. Strong side effects such as severe degeneration of the seminiferous epithelium in rats or degeneration of germ cells and a decrease in the testicular weight in dogs have been observed after subacute oral administration of **506** or **627**[619]. According to the reactivity of **567** towards nucleophiles (Table 2), the formation of an *N,S*-acetal by a thiol group of the enzyme should inactivate the enzyme system (for a mechanistic consideration see Ref. 625). Furthermore, the activity of monoamine oxidase in the liver was significantly decreased by **506**. Semiaminal **575** was claimed to have nicotine antagonistic activity[623]. The inhibition of acetaldehyde dehydrogenase was also observed with aminocyclopropanes **635a** and **635b**, possessing no α-hydroxy function[626].

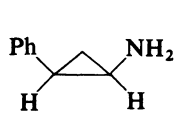
2. *Aminocyclopropanes with an aryl or heteroaryl moiety as MAO inhibitors*

The most outstanding effect of *trans*-2-phenylcyclopropylamine (**5**) (generic names: tranylcypromine, transamine) is the inhibition of monoamine oxidase (MAO)[611, 612, 627]. The sulfuric acid salt of **5** (Parnate^R, Jatrosom^R) is used as an antidepressant drug, and best results were achieved in chronic neurotic patients. (+)-(**5**) was reported to be also effective as an adjuvant in Parkinson's disease therapy[628]. Differences of activities of the pure enantiomers[611, 629–653] (for a minireview see Ref. 629; for resolution of racemic **5** see Refs 42, 103, 160, 654, 655; for g.c. separation of racemic **5** as *N*-trifluoracetyl-L-prolyl derivative, see Ref. 656) and the *trans–cis* diastereomers **5**/**628**[611, 657] have been studied as well as the selectivities of **5** on inhibition of MAO type A and B (e.g. Refs 637, 638, 658–674). (+)-(**5**) showed stronger inhibition of platelet MAO[630–632] (dopamine[633, 634], norepinephrine[635] oxidation), stronger antidepressant activity and more side effects[630, 631] (double-blind controlled study; for comparison see also Ref. 636) than (−)-(**5**). Furthermore, it was pointed out that (+)-(**5**) influences mainly tryptaminergic neurotransmission while (−)-(**5**) affects primarily catecholaminergic neurotransmission[629]. No differences between (+)- and (−)-(**5**) were observed in anticholinesterase activity[647]. The *cis*-isomer (**628**) generally showed lower activities with respect to *trans*-(**5**)[87, 611, 657]. Strong interest in tranylcypromine led to more than 700 publications between 1965 and 1985 dealing with **5**.

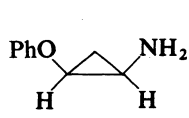
Variation of substituents in structural subunits of **5**, e.g. by introducing substituents in the amino moiety, the phenyl or the cyclopropyl moiety, generally caused a decreasing effect in MAO inhibition[611]. Only *cis*-(**629**) was found to have a similar potency as **5**; interestingly in this case the corresponding *trans* compound was less active.



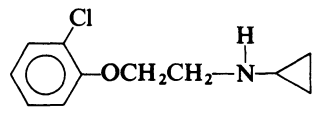
(**5**)



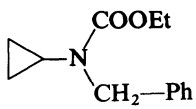
(**628**)



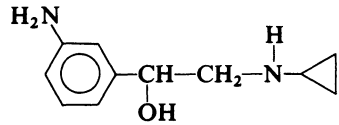
(**629**)



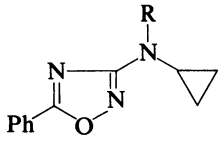
(**630**)



(**631**)



(**632**)



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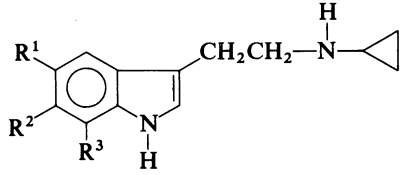


(634)

R^1–R^3 = H,
R^1, R^2 = H, R^3 = OMe
R^1, R^3 = H, R^2 = OMe
R^1, R^2 = OMe, R^3 = H

Aminocyclopropyl compounds **630** (Lilly 51641) and **631** (Encyprat) have also been tested clinically as antidepressant drugs[611]. **630** turned out to be a fairly selective inhibitor for type A MAO, e.g. Refs 637, 638, 658, 669, 670, 675, 676; a similar behavior was found for the corresponding iodo compound (**630**, I instead of Cl)[677]. Derivatives **632** (AB 15)[678–681], **633**[682, 683] and **634**[684–690] are further examples for compounds with remarkable inhibitory effects for MAO.

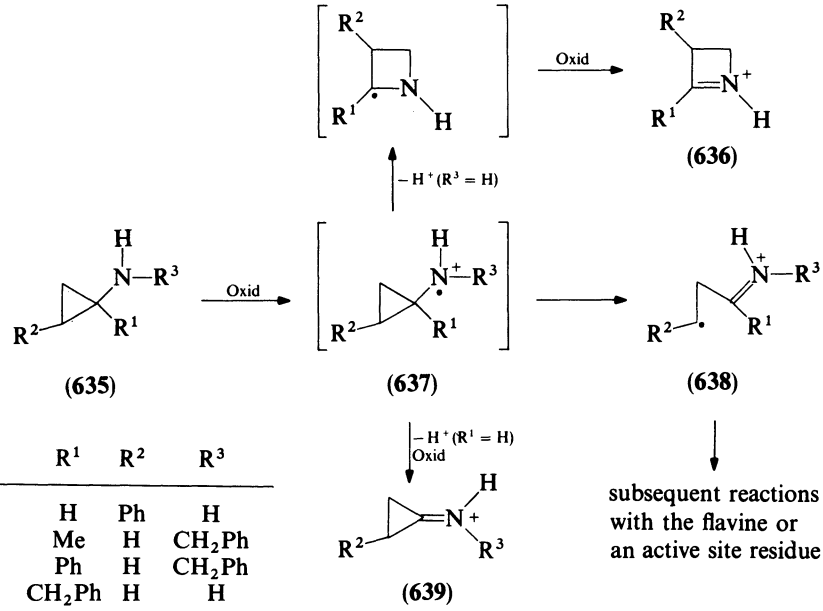
Aminocyclopropanes (**634** and **635a–d**) also deactivated cytochrome P-450 enzyme[691–696]. By using labeled compounds **635**, it was established that deactivation of MAO or cytochrome P-450 occurred by a suicide deactivation type[148, 548, 685, 686, 688, 693–702].

Radical cation **637** was indicated to be the first intermediate in the oxidation process of **635**[148, 595, 691, 692, 696, 699, 700]; among the subsequent species (**636**, **638** and **639**) radical cation **638** plays the most important role in the inhibition process. Tranylcypromin **635a** (= **5**) was elucidated to inactivate MAO by formation of a labile covalent bond between **638** and an active site residue (Scheme 17)[595, 698]. (1-Methylcyclopropyl)benzylamine (**635b**) was shown to be an irreversible mechanism-based inactivator of MAO: Unlike **635a**, it formed a stable covalent bond to the covalently bound FAD cofactor[148]. Inactivation of MAO by **635c** occurred by covalent bond formation to both the flavin cofactor (stable adduct) and to an active site residue (labile adduct) in a 1:7 ratio[699]. Cyclopropylamines possessing a secondary or tertiary benzyl moiety at the *N*-atom were included in these mechanistic studies[700]. Mechanisms of inactivation of cytochrome P-450 and monoamine oxidase were reviewed by Tullman and Hanzlik[696]. The inhibitor effects of aminocyclopropanes against P-450 enzyme were compared with those of other cyclopropane derivatives[703].

1-Substituted cyclopropylamines as 1-benzylcyclopropylamine (**635d**), inhibited MAO less strongly *in vivo*; it was found that this type of cyclopropylamines showed preferentially anorectic activity[76, 611].

3. Aminocyclopropane-carboxylic acid derivatives

Aminocyclopropane carboxylic acid (**6**) has been detected in several plant tissues[9, 704]; a procedure for preparing **6** from agricultural wastes, by extraction with a diluted solution of sulfosalicylic acid, has been described[705]. **6** was established to be an intermediate product in ethylene biosynthesis[706–708]. Ethylene acts as a phytohormone which is involved in many metabolic processes in plants, e.g. in ripening, in stress situations or after wounding (see review[709] and references cited therein). Natural **6** is formed from methionine via sulfonium salt (**640**); only *S,S*-(**640**) acted as a substrate for aminocyclopropanecarboxylate synthase, the *S,R* and *R,R* isomers of **640** were inactive as substrates[710]. **6** can be



	R^1	R^2	R^3
a	H	Ph	H
b	Me	H	CH_2Ph
c	Ph	H	CH_2Ph
d	CH_2Ph	H	H

SCHEME 17

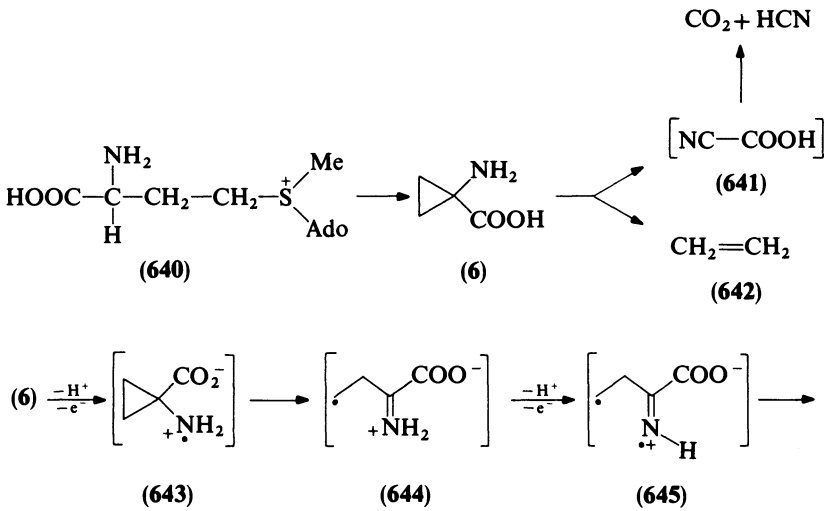
converted into ethylene in the presence of pyridoxal phosphate, $MnCl_2$ and H_2O_2 at pH 11.5, giving an assay for detection of **6** in extracts of fruits[711]; for detection of **6** by NaOCl oxidation see Ref. 569. *In vivo* synthesis of **6** and *in vivo* conversion of **6** into ethylene are controlled by several regulators[711]. ESR has provided evidence for the involvement of the superoxide anion radical O_2^- in the ethylene generation by microsomal membranes[570]. The mechanism of ethylene formation from **6** was studied with a 1,2-*cis*-dideuterated compound[320, 326] which gave a 1:1 mixture of *cis*- and *trans*-dideuterioethylene. The partial loss of *cis* configuration was discussed in terms of radical intermediates **643–645**, which were modeled through electrochemical or $KMnO_4$, $CuSO_4$ or K_2FeO_4 oxidation of **6**[320, 571]. In addition to ethylene (**642**), cyanide and CO_2 (from **641**) are formed as byproducts[320, 712] (see also Refs 324, 326, 713); the cyanide is metabolized to asparagine via β-cyanoalanine[712] (Scheme 18).

The malonyl derivative **646** plays an important role in the metabolism of **6** (e.g. Refs 715–719). Possible applications of **6** or other ethylene producing reagents such as plant growth regulators (e.g. Refs 318, 720–725), in the facilitation of the falling and harvesting of olives[726] or further fields[727] are described in review Ref. 709.

6 has also been applied as an amino acid component, e.g. in the synthesis of enkephalin[728–731] or oxytocin[732] and analogous peptides.

Aminocyclopropane carboxylic acid deaminase, obtained from *Pseudomonas* bacteria, decomposes **6** to ammonia and 2-ketobutyrate (**647**)[34, 143, 733–735]. By using *R*- and *S*-2,2-dideuterio-(**6**) it was shown that the methyl group in **647** has its specific origin in the pro-*S* methylene moiety of **6**[34, 143].

(+)-(1*S*,2*S*)-1-amino-2-ethylcyclopropane-1-carboxylic acid (**505**)[27, 33, 387, 555], coronamic acid, was found to be a component of the bacterial phytotoxin coronatine (**648**)[736–746] (a short review is given in Ref. 566). **648** was isolated from the culture fluid of virulent isolates of *Pseudomonas syringae pv. atropurpurea*. **648** is also produced by two

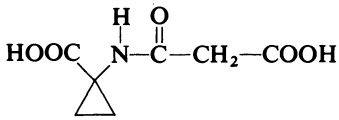


Ado = Adenosyl

SCHEME 18

other pathovars, *Glycinea* and *Morsprunorum*. Coronatine induces chlorosis on the leaves of Italian ryegrass; it was shown that **648** is not a host-specific toxin. **648** also effected a hypertrophic response of potato tubers.

Influences on the activity of **648** which were caused by changing the configuration of **505** or by using alkyl analogs instead of the ethyl group in **505** have been studied[742].



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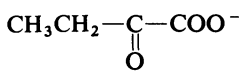

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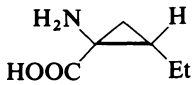

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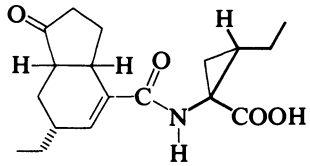

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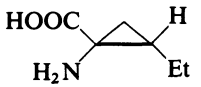

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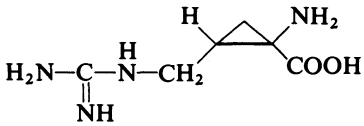


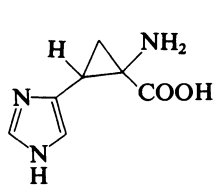
(650)

Biochemical reactions of 1-amino-2-ethylcyclopropane-1-carboxylic acid showed strong stereoselectivity. Thus, ring-opening to 2-ketohexanoate was observed only with the (1*S*, 2*S*)-isomer (**505**)[34, 747]. On the other hand, cycloelimination to give butene by the ethylene forming enzyme in apples or pea epicotyls was performed preferentially with allocoronamic acid (**649**), the (1*R*, 2*S*)-isomer[568, 748]. Pea epicotyl enzyme (cell-free system) catalyzed the formation of 1-butene for all stereoisomers (i.e. **505** and **649**)[748, 749].

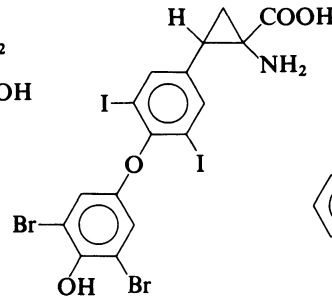
1*R*-Coronamic acid (**505**) and 1*R*-allocoronamic acid (**649**) were more effectively converted to the 1-malonyl derivative than the two 1*S*-stereoisomers[750, 751]. From this stereoselectivity it was deduced that aminocyclopropanecarboxylic acid (**6**) is recognized as a D-amino acid by malonyl transferase. For resolution of racemic 2-alkyl-1-aminocyclopropane-1-carboxylic acids see Refs 27, 33, 752.

Carnosadine (**650**), a guanidinomethyl aminocyclopropane carboxylic acid has been isolated from red algae *G. carnosa*[753].

In the series of cyclopropane amino acids, compounds **651**, **652** and **653** have also been studied. The cyclopropyl analogs **651** and **652** showed distinctly lower activity than the corresponding amino acids histidine and thyroxine[63, 611]. Compounds **653** were tested for their behavior towards several hydroxylase, aminotransferase and decarboxylase enzyme systems[118, 303, 754, 755]. The *cis* isomer had no inhibitory effect[118].



(**651**)



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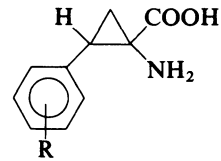
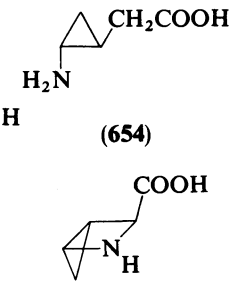


(**653**)



(**654**)

(**121**)

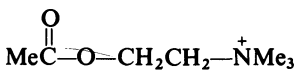
γ-Aminobutyric acid (GABA) is a neurotransmitter within the vertebral central nervous system **654** was found to inhibit reversibly GABA-transaminase and -aminopyruvate transaminase[122, 130]. Amino acid **121**, produced by *Streptomyces omyceticus* SF-1836, showed antibiotic activity against bacterial leaf blight of rice plant[714a–d].

4. Aminocyclopropane derivatives in receptor studies and drug design

Conformation effects of an active compound play an important role in enzyme substrate complexes. A three-membered ring between the active functional groups causes conformational rigidity. Thus 'cyclopropylogs' of active compounds were used to study receptor geometries and to obtain information on drug activity.

Among the various 'cyclopropylogs' of acetylcholine (**655**), the *trans*(+)-2-acetoxycyclopropyltrimethylammonium iodide (**656**) showed strong muscarinic activity[13, 14, 611, 756–760]. The *cis* isomer (**657**) exhibited only 0.3% of the muscarinic potency of **656**[13]. For both compounds **656** and **657** complete lack of nicotine agonist effects were reported. The functional groups in **656** have the same steric structure as in L (+)-muscarine or (+)-(*S*)-β-methylcholine, two powerful muscarinic reagents[611]. **656** was applied in the development of drug–receptor interaction models[759, 761, 762]. On the other hand, the homologous derivatives **658** and **659** showed a considerable degree of nicotinic

effect, the *trans* isomer (**659**) being about ten times as potent as the *cis* isomer (**658**)[82]. **658** and **659**, however, demonstrated no appreciable muscarinic effects[82]. *Cis*- and *trans*-benzyloxy compounds **661** and **662**, respectively, have been tested as cyclopropylogs of choline ethers (**660**)[611, 763].



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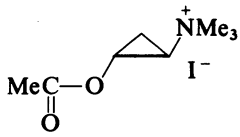

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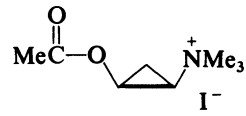

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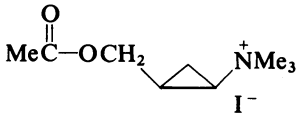

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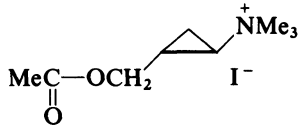

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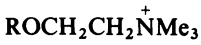
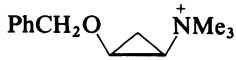


(**660**)



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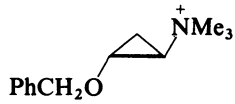

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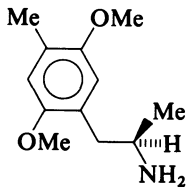

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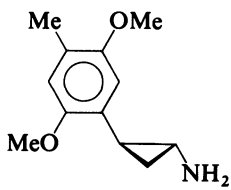

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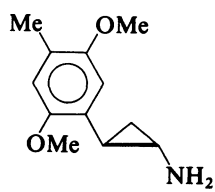


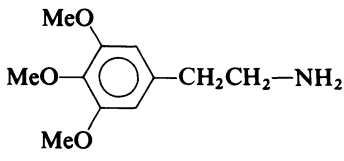
(**665**)

A receptor model for hallucinogenic amines (e.g. phenethylamine and tryptamine hallucinogens) was tested by **664** and **665**, the cyclopropylogs of **663**[114, 140, 764–766]. The (−)(1*R*, 2*S*)-isomer, **664**, possessed stereoselective LSD-like activity with respect to the (1*S*, 2*R*)-enantiomer **665**. Influences on the activity of compounds of type **664**/**665** with respect to constitutional variations have also been studied[767].

Strong differences in activity were observed for the *cis* and *trans* diastereomers **667** and **668** which are the cyclopropyl analogs of mescaline (**666**)[75, 768, 769]. The *trans* isomer (**668**) effected the mescaline-induced syndrome in rats, whereas the *cis* isomer (**667**) was almost inactive at comparable doses[768].

Adrenergic and dopaminergic properties of **669** and derivatives, e.g. **670** and **671** (see Table 1), which are rigid analogs of dopamine, have been investigated[93, 113, 280, 770, 771].

Bis(dioxopiperazino)propane (**672**), ICRF-159, possesses antitumor activity[772, 773]. **673** and **674**, cyclopropylogs of **672**, showed different behavior towards a hamster lung adenocarcinoma (LG 1002). *Cis*-(**673**) significantly inhibited the development of lung metastases with no effect on primary tumor growth. The *trans* isomer (**674**), on the other



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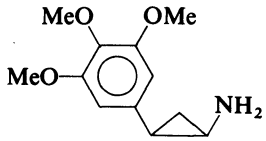

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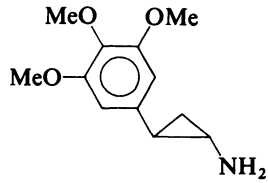

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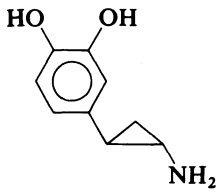

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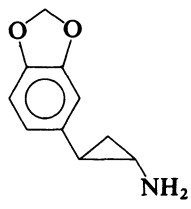

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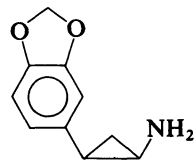

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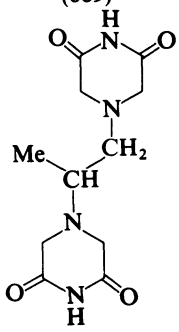

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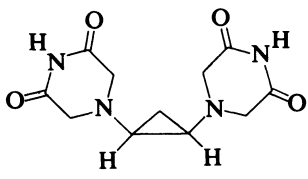

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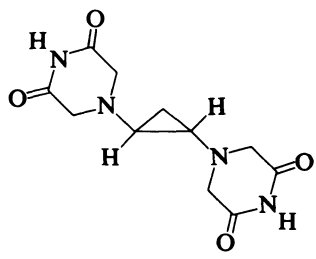
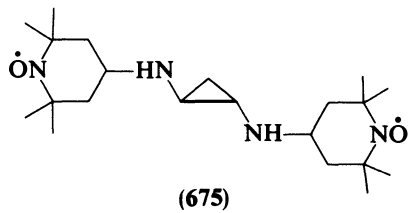


(674)

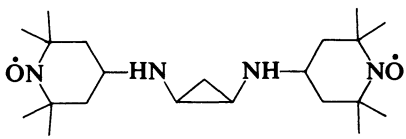
hand, appeared to stimulate the growth of lung metastases and of the primary tumor[104,111,557,774]. This demonstrates the preferential interaction of **672** in a *syn*-conformation.

Differences in sensitization of hypoxic Chinese hamster cells to γ-rays by **675** or **676** and the conformationally unrestricted **677** are reported[775].

The antibacterial potencies of **678a** and **678b** were shown to diminish considerably from their penam analogs penicillin G (**679a**) and mecillinam (**679b**)[776]. Despite this, **678a** was a

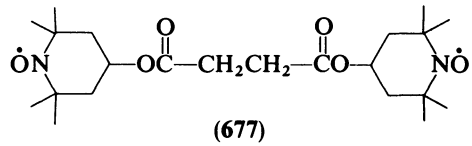


(675)



(676)

substrate for bacterial β-lactamases and compounds **678c** and **678d** were found to be β-lactamase inhibitors. From these studies with **678a** and **678b** the biologically active conformation of penicillin antibacterials was deduced.



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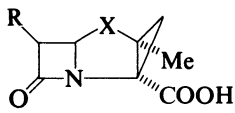

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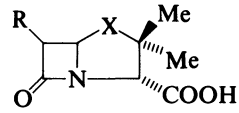
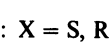
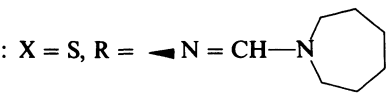
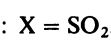


(679)

(678a)/(679a): X = S, R = 

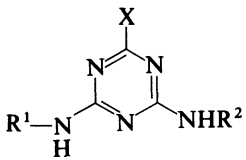
(678b)/(679b): X = S, R = 

(678c) : X = S, R = 

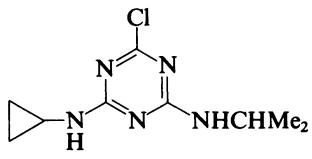
(678d) : X = SO_2, R = H or

5. The aminocyclopropyl group in pesticides, antiviral and antibacterial agents

Aminotriazines of the general formula **680** are useful herbicides[777]. In some cases a cyclopropyl group instead of other alkyl moieties in **680** led to increased effectiveness. Thus, compound **681**[778–784] (generic name: cyprazine; trademark: Outfox^R) was reported to be superior to other chlorodiaminotriazines (**680**, X = Cl) in controlling certain grass weeds in corn[782]. Application of **681** in combination with other herbicidal components has been investigated[785–794] (e.g. Prefox^R: mixture of **681** and $Et_2NCSSEt$). **682** (procyazine, Cycle^R) exhibited selective activities against grasses and weeds in corn, cereals and leguminoses[777, 795–801]. Herbicidal properties of a lot of cyclopropylaminotriazines (**680**, R^1 = *c*-C_3H_5), in which X represents a methoxy[802–805], a methylthio[804–812] (rapidly acting against seawater algae[811]), an azido[804, 809, 810, 812–824] or a chlorine[825–827] moiety (variation of R^2-alkyl substituents) have been investigated.



(680)



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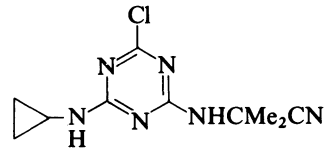
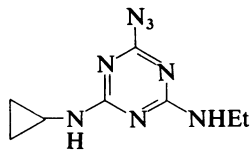


(682)

X = Hal, OR, SR, NR_2, N_3



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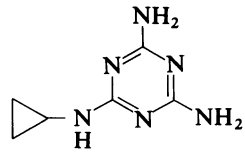
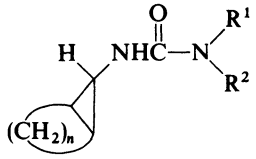


(684)

The azido derivative **683** (CGA 19255) had herbicidal[813] and even better insecticidal[815–824] activity. **683** prevented the development of the larvae of the house fly (*Musca domestica*); it was tested successfully as a poultry feed-through larvicide[815–818,823,824]. **684** (CGA 72622; cyromazine, Larvadex^R), a metabolite of **683**[823,824], proved to be better suitable as a larvicide[828–852]. It inhibited growth of a great variety of Diptera insect larvae (e.g. house fly, yellow fever mosquito, face fly, sheep blowfly, fall army worm). Additionally, **684** was used as anthelmintic[835]. **684** is applied as a food additive for domestic or livestock animals or by spraying it on manure surface. Larvicidal properties of formamido[853–855] and formamidino[856] derivatives of **684** have been tested. The bacterial degradation of **684** was investigated[857].

Carboxamides and ureas are classes of compounds which embrace a large number of commercial and experimental pesticides. As expected, carboxamide[396,858,859], thiocarboxamide[860,861], urea[21,24,862–867] and aminoquinone[868] derivatives possessing a *N*-cyclopropyl moiety have also been studied. Compounds **685–689** should serve as examples for these investigations. **685**[21,24], **686**[863–865] and **687**, R^1 = alkyl, R^3 = phenyl)[859] showed herbicidal activity; for **687** ($R^1 = R^3 = H$)[858] and **688**[396] fungicidal properties were reported. **689**[860,861] finally was used for controlling insect larvae especially of the Noctuidae (Phalaenidae) family. Urea (**690**) was reported to be an antagonist against inducers of chlorophyll retention in senescing leaf disks[869].



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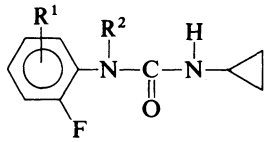

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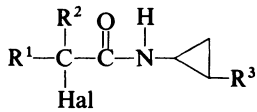

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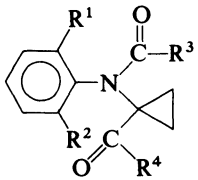

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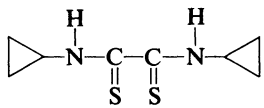

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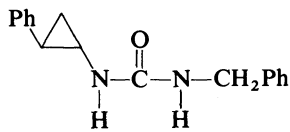


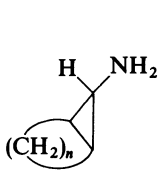
(690)

Antiviral activity was established for bicyclo[n.1.0]alkylamines (**691**)[16,19]. Bifunctional ammonium salts of type **692** were claimed to be useful as disinfectants[17,18]; application of the bicyclo[n.1.0]alkyl ammonium group as counterion in penicillin salts has been tested, e.g. Ref. 341. A *N*-cyclopropyl moiety is also part of the antibacterial agent ciprofloxacin (BAY 09867) (**693**)[870–888]. **693** shows strong antibacterial activity especially against Enterobacteriaceae; it was considerably more active than other agents tested[870,876,878].

The antibacterial potency of similar *N*-cyclopropyl derivatives having a pyridino[889,890] or a pyrimidino[891] instead of the benzo ring system, or other amino groups instead of the piperazino moiety[888] in **693** has been established.

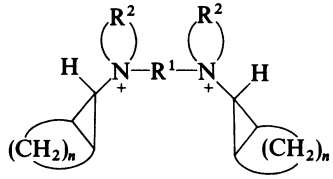
6. The aminocyclopropyl group in derivatives of miscellaneous activities

Adenosine (**694**, X = CH_2OH) and derivatives of **694** inhibit adrenergic transmission presynaptically. Therefore these substances are useful as cardiovascular stimulating



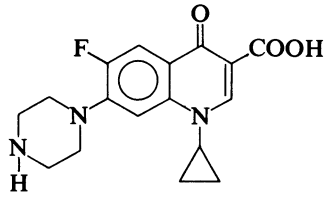
(691)

$n = 3, 5, 6$



(692)

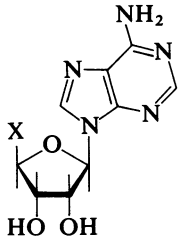
$R^1 = (CH_2)_{4-6}$, $R^2 = (CH_2)_{4,5}$



(693)

agents. Among these derivatives the *N*-cyclopropylcarboxamide **695** was proved to be one of the most potent compounds[892-903]. As a consequence, **695** was often used for experimental investigations. Inosine[904] and imidazole[905,906] analogs of **695** showed similar effects.

Compounds **696**[907,908] and **697**[909-912] are further examples for antihypertensive agents, in which a cyclopropylamino group is involved. Diuretic, hypnotic and anorectic effects have been claimed for **697**, too[909,912]. Aminocyclopropanes with tranquillizing properties[255,426] or as part of a tranquillizing system[913,914] have been reported. Anti-inflammatory activity was found for compounds **698**[915,916] and **699**[917]; for further examples see Refs 77, 391. Analgesic effectiveness has been established for some



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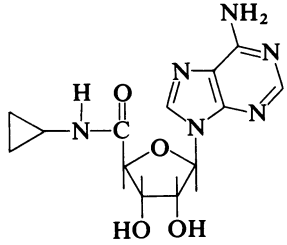

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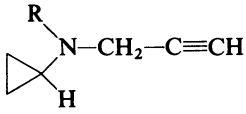

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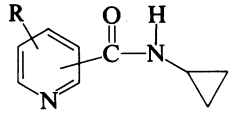
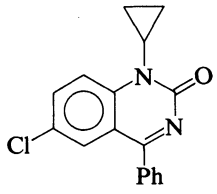


(697)

bicyclo[n.1.0]alkylamines[129,150]; e.g. 7-*exo*-bicyclo[4.1.0]heptylamine (**585**)[150]. The corresponding bicyclo[4.1.0]heptene compounds proved to be rather toxic[150].

N-Cyclopropylamides **700**[918], **701**[919-921] and **702**[922] exhibited anticonvulsive properties besides other effects (e.g. antiarrhythmic effects of **701**[919-921]; another arrhythmic agent is reported in Ref. 923). *N*-Cyclopropyl derivatives (**703**) could be used as selective β_1- but not β_2-receptor blockers[924].

The mutagenicity of *N*-nitrosocyclopropylamino derivatives of type **704** and **705** has been compared with related nitroso compounds[925-927]. It was found that cyclopropylnitrosamines (**705**) were much more effective mutagens than the corresponding allyl derivatives[927].



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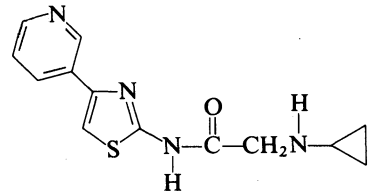

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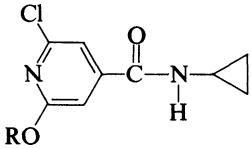

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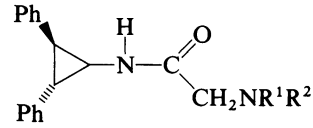

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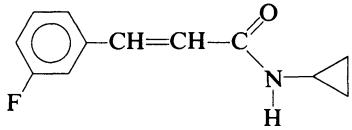

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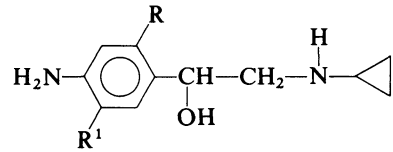

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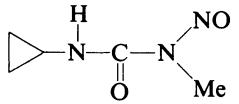

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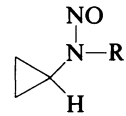

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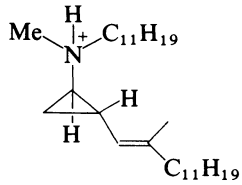
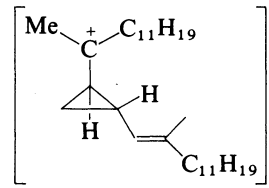


(706)



(707)

Ammonium salt (**706**) was used to mimic the topological and electrostatic properties of cation **707**, which was suggested to be an intermediate in squalene biosynthesis[135]. **706** turned out to inhibit squalene synthetase only in combination with pyrophosphate[135].

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CHAPTER **23**

The chemistry of cyclopropanones

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I. INTRODUCTION

Because they incorporate elements of exceptional reactivity in a small carbon skeleton, cyclopropanones have long been of special interest to organic chemists. The unique bonding characteristics and the factors which play a role in the carbon–carbon cleavages during reactions of this system have been investigated by chemists from the standpoint of theory and reaction mechanism, while synthetic organic chemists have regarded these ketones and their derivatives as potential sources of reactive three-carbon fragments.

Cyclopropanones are usually not isolated as discrete entities since they rapidly undergo polymerization or ring-opening, especially in the presence of acids or bases. For this reason, much of the chemistry of cyclopropanone and its derivatives has been observed through the behavior of transient intermediates such as hemiketals formed *in situ* from precursors[1, 2].

In this chapter, we will review methods for preparing cyclopropanones, their physical and spectroscopic properties, and the nature of their reactions with nucleophiles, electrophiles and in cycloaddition processes. Another part of the chapter will deal with cyclopropanone equivalents, 1,1-disubstituted systems which under certain conditions may provide carbonyl-related derivatives of the parent ketones. We will also discuss the role of cyclopropanones in biological phenomena and cite specific examples of the use of cyclopropanone intermediates as key units in the synthesis of natural products.

Our review of cyclopropanone chemistry is intended to be illustrative of the current state of the field without attempting to be exhaustive in cataloging all examples of the formation of this system and all types of reactivity. For a more detailed coverage of aspects of this subject, the reader is referred to earlier reviews by Turro[3] and by Wasserman and coworkers[4].

A significant advance in the study of cyclopropanones resulted from studies by the Turro[5] and the de Boer[6] groups on the formation of cyclopropanones in solution by the reaction of ketenes with diazoalkanes. These investigators found that it is possible to store the parent ketone only for short periods at low temperature because of its unusual reactivity and propensity for polymerization. Subsequent work has shown that cyclopropanone seems to show chemical behavior similar to that of ketene. Thus, it is attacked by nucleophilic species such as water, alcohol and amines and reacts rapidly with itself to form

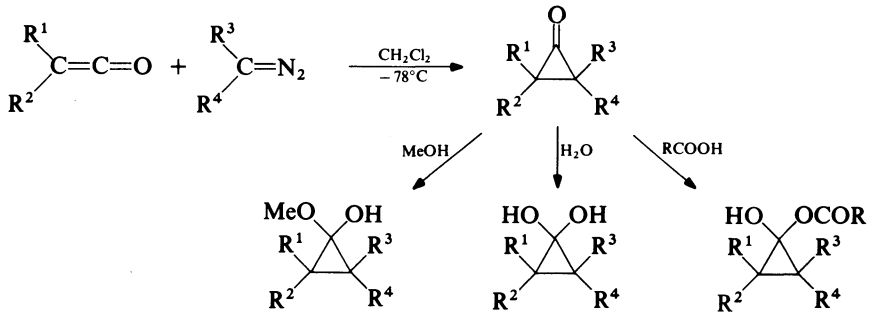
polymers. Table 1 lists examples of cyclopropanones which have been studied to date. Some of these ketones have been isolated as discrete species, but most have been generated in solution.

II. PREPARATION OF CYCLOPROPANONES AND THEIR PRECURSORS

Because of their instability, cyclopropanones have been isolated in only a few cases, and methods for preparing the pure ketones are very limited. Among these are the addition of diazoalkanes to ketenes at low temperature[5-7], potassium *t*-butoxide elimination of highly substituted α-bromoketones[8], photochemical decarbonylation of cyclobutane-1,3-diones[9-11] and ring-closure of 1,3-dihalo ketones[12, 13]. Other methods exist for formation of cyclopropanones as intermediates which may be trapped by addition of nucleophiles to the carbonyl group. These methods include electrosynthesis[13], the Favorskii reaction[14] and the Ruhlmann reduction of β-chloropropionyl chloride[15].

A. Diazoalkane–Ketene Reactions

By far the most useful method for making cyclopropanones has involved the addition of diazoalkanes to ketenes, a reaction which was first explored by Turro and Hammond[5] and by de Boer and coworkers[6]. The cyclopropanone formed (Scheme 1) is immediately trapped by the addition of a nucleophile such as water, an alcohol or carboxylic acid. Turro found that although cyclopropanone itself is not isolable, a dilute solution of this ketone (0.5–0.8 M) may be stored at −78°C for several days.

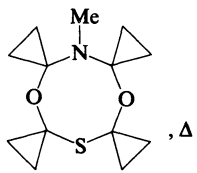
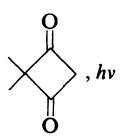
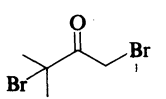


SCHEME 1

In general, the cyclopropanones which have been prepared by the above routes are too unstable to be isolated, and are therefore usually trapped by alcohols, amines or as other carbonyl addition products. One particularly useful, stable cyclopropanone source is the acetic acid addition product reported by van Tilborg[16]. This material can easily be purified, and readily yields the parent ketone *in situ* on reaction with nucleophiles. A summary of cyclopropanones prepared by this route has been reported[4].

A recent example of the preparation of a silylated and germylated cyclopropanone has been provided by Russian workers[17] who added diazomethane in ether or methylene chloride at −130 °C to an equimolar amount of trimethylsilyl and trimethylgermylketene. The authors were able to obtain PMR spectra of the parent ketones which show an ABC system of cyclopropane ring protons at δ 0.8–1.8 ppm. These products react with methanol to form hemiketals and undergo ring expansion with excess diazomethane to form the corresponding cyclobutanone derivatives.

TABLE 1. Cyclopropanones isolated or characterized in solution

Cyclopropanone	Method of preparation	Solvent	Temp. (°C)	Yield (%)	State in which studied	Method of characterization	Ref.
		$CDCl_3$ CD_3NO_2, or $CDCl_3/C_5D_5N$	40–70	30–60	Solution	NMR	174
	$CH_2N_2 + CH_2C{=}O$	CH_2Cl_2	−78	50–60	Solution	IR, NMR, UV, reactions	5
	$CH_2N_2 + CH_2C{=}O$	$CHCl_3$; propane; $CFCl_3$	−78	50	Impure liquid, stable few days at liq. N_2 temp.	IR, NMR, reactions	6
	$CH_2N_2 + CH_2C{=}O$	$CFCl_3$	−78	—	Gas-phase mixture	microwave	45
	$CH_2N_2 + CH_2C{=}O$	N_2 (solid)	−253	—	N_2 matrix; gas-phase mixture	IR	175
	$CH_2N_2 + CH_2C{=}O$	CH_2Cl_2	−78	75	Solution	reactions	16
	$MeCHN_2 + CH_2C{=}O$	CH_2Cl_2	−78	—	0.4 M solution	IR, NMR	11
	$CH_2N_2 + Me_2C{=}C{=}O$	CH_2Cl_2	−78	> 93	Solution	IR, NMR, UV, reactions	99
		—	—	'Low'	—	IR	11
		DMF	—	—	—	IR	129, 176

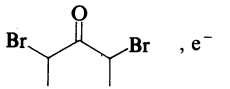
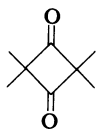
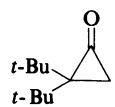
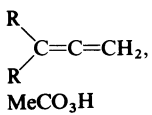
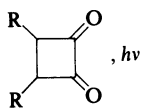
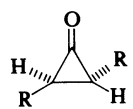
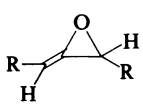
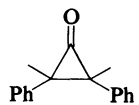
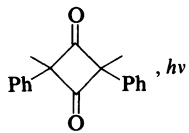
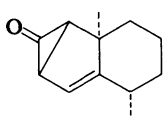
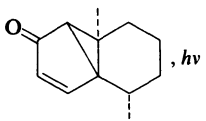
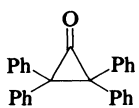
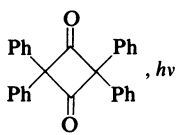
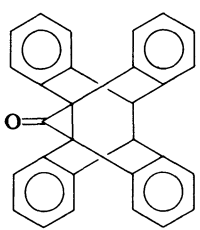
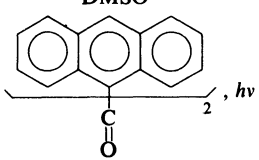
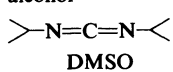
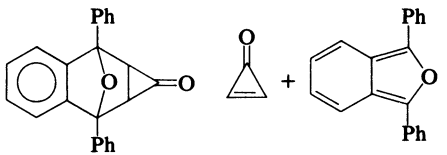
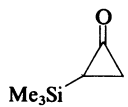
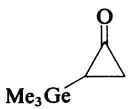
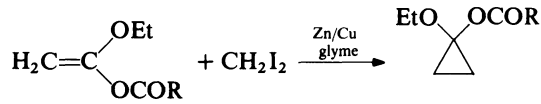
	 , e^-	—	—	30–70			129, 176
	Me_2CN_2 + 	CH_2Cl_2	−78	> 60	Solution	IR, NMR, reactions	95
	 , *hv*	Pentane	36	—	Solution	IR, reactions	9
		CH_2Cl_2	0	—	Solution	IR, NMR, UV, reactions	11
		N_2 (solid)	−269	—	Matrix	IR	177
		Cyclohexane	24	—	Solution	IR	177
		CH_2Cl_2	—	—	Solid, m.p. 41–43°C	Analysis, IR, NMR, UV mass spec., reactions	36
	(a)  , *hv*	—	—	—	—	—	178
	(b) $RCHBrCOCH_2R$, base	—	—	20–40	Solid, m.p. 24–26°C	Analysis, IR, NMR, UV, mass spec., reactions	8
R = *t*-Bu	(c) 	—	100	—	—	IR, UV	31

TABLE 1. *Continued*

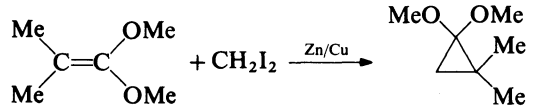
Cyclopropanone	Method of preparation	Solvent	Temp. (°C)	Yield (%)	State in which studied	Method of characterization	Ref.
		—	—	'Low'	—	IR	11
		Film	−190	—	Decomposes −115°C	IR, reactions	80
		—	—	'Low'	—	IR	11
	Oxidation of corresp. alcohol	DMSO	—	—	Solid, m.p. 240–260 °C, dec.	IR, NMR, mass spec., reactions	179
		—	—	—	—	—	3

	—	—	100	Solid, m.p. 151–153 °C	IR, NMR, mass spec., methanol addition	79
	$CH_2N_2 + Me_3SiCHC{=}O$	ether, or CH_2Cl_2	−130	50	b.p. 34–35 °C/6 mm	IR, NMR, analysis	17
	$CH_2N_2 + Me_3GeCHC{=}O$	ether, or CH_2Cl_2	−130	50	b.p. 45–47 °C/5 mm	IR, NMR, analysis	17

Use of the Simmons–Smith reagent[18] for the formation of cyclopropanone precursors has been reported in the case of ethoxyvinyl carboxylates[19a] (**1**) and ketene ketals[19b] (**2**) (Scheme 2). Using 1-ethoxyvinyl acetate and benzoate, it was found that the zinc iodide generated in the reaction tends to favor opening of the cyclopropane ring. However use of glyme as a solvent prevents attack on the ring by this Lewis acid since the zinc salt is insoluble in that medium[20].



(1) **a**, R = Me
b, R = Ph



(2)

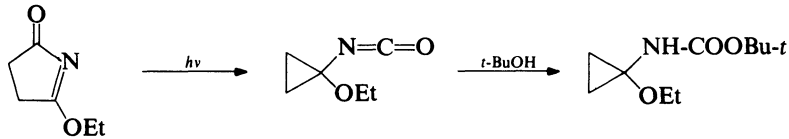
SCHEME 2

Recently it has been shown that cyclopropanone ketals and hemiketals can be prepared conveniently by cyclopropanation of ketene alkylsilyl ketals or ketene disilyl ketals with diethylzinc-methylene iodide in ether[21].

B. Photochemical Processes

The photolysis of 1,3-cyclobutanediones has been investigated as an entry into the chemistry of cyclopropanones[11]. Studies on tetramethylcyclobutanedione have shown that irradiation with light of $\lambda > 300$ nm at very low temperature in an inert medium (nitrogen matrix) formed cyclopropanone and dimethylketene as products identified by IR spectroscopy. An extensive review of this subject has been provided by Quast and Fuss[22]. In general, the yields are not good due to side reactions under the conditions of photolysis.

Koch has reported that the irradiation of 2-ethoxypyrrolidin-5-one (**3**) and related derivatives yields 1-ethoxycyclopropyl isocyanates (**4**) or the corresponding *t*-butyl carbamates[23, 24] (**5**) (equation 1). This procedure has been developed into a general



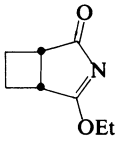
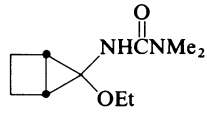
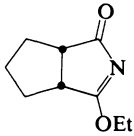
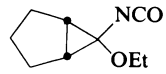
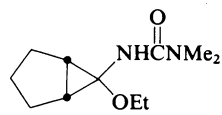
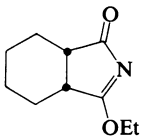
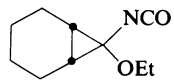
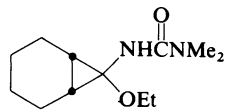
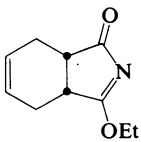
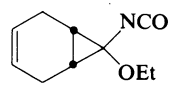
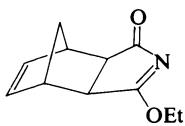
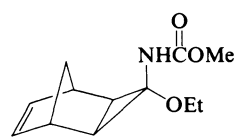
(1)

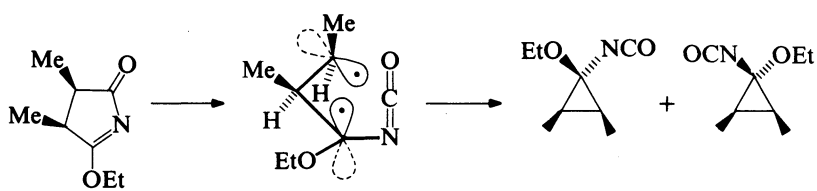
(3) **(4)** **(5)**

method for the formation of functionalized bicyclo[n.1.0] systems[25]. Table 2 lists some of the bicyclic systems prepared in this way.

The photorearrangement appears to be highly stereospecific with respect to carbon-4 and stereoselective with respect to carbon-2[26]. The authors favor a diradical mechanism[27] (Scheme 3).

Table 2. Bicyclic systems prepared by photolysis of 2-ethoxypyrrolidin-5-ones

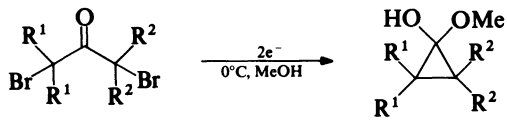
Pyrrolidinone	Photoproduct or derivative	Isolated Yield (%)
		43
		76
		56
		64
		56
		53
		53



SCHEME 3

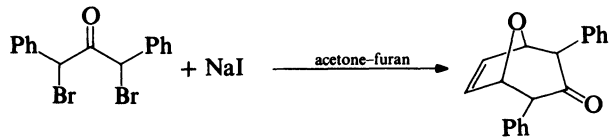
C. Ring-closure by Dehalogenation or Dehydrohalogenation

1,3-Dehalogenation has provided routes to cyclopropanones which may then be trapped in the form of hemiketals or cycloaddition products. Thus, electrolytic reduction of 1,3-dibromo-2-propanones served as a method for preparing the derivatives **6** and **7** as shown in equation 2[13]. In a related reaction, treatment of α,α′-dibromobenzyl ketone with sodium iodide in acetone in the presence of furan yielded the cycloadduct **8** (equation 3)[28].



(2)

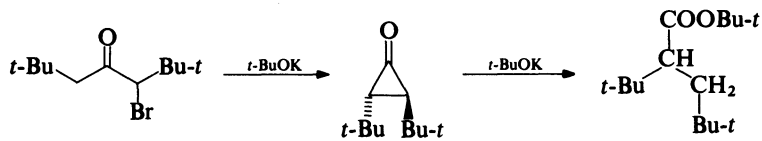
(**6**) $R^1 = R^2 = Me$
(**7**) $R^1 = H$, $R^2 = Me$



(3)

(**8**)

Illustrative of the dehydrohalogenation pathway, the formation of *trans*-1,2-di-*t*-butylcyclopropanone reported earlier by Greene and coworkers has now been described in detail[8]. The reaction may be carried out heterogeneously in ether, or homogeneously in *t*-butyl alcohol, conditions which correspond to those of the well-known Favorskii reaction. In this reaction it is crucial to use exactly one equivalent of base, since even a small excess results in complete conversion to the ester[29] (equation 4).



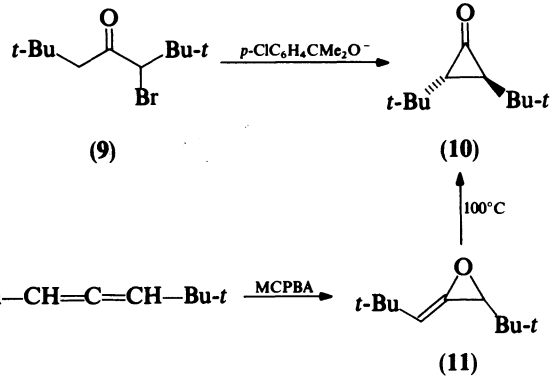
(4)

(**9**) (**10**)

Classic work by Loftfield[30] on the Favorskii reaction showed that cyclopropanones are intermediates in the base-induced rearrangement of α-haloketones (Scheme 4). Isolation of such an intermediate was accomplished in the reaction of the sterically hindered α-bromodineopentyl ketone (**9**) with potassium *p*-chlorophenyldimethylcarbinolate. The identity of the product (**10**), *trans*-2,3-di-*t*-butylcyclopropanone, was established by independent synthesis of 1,3-di-*t*-butylallene oxide (**11**) which underwent valence isomerization to (**10**)[31].

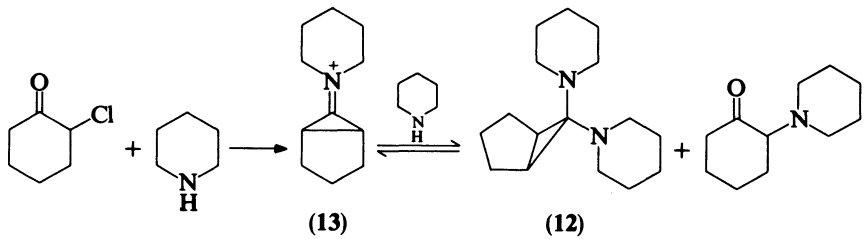
An unusual example of a Favorskii type of reaction is found in the reaction of α-chlorocyclohexanone with piperidine leading to the formation of 6,6-dipiperidinobicyclo[3.1.0]hexane (**12**)[32]. The reaction takes place most probably through the cyclopropanone iminium salt (**13**) as shown in equation 5.

Exploration of the chemistry of cyclopropanimines has been carried out by Quast and coworkers during extensive studies on α-bromoketimines[33]. 1,3-Elimination of hydrogen bromide from **14** by excess potassium *t*-butoxide in THF yields the imines as colorless oils or low melting solids (equation 6). As shown by their ^{1}H- and ^{13}C-NMR spectra, these

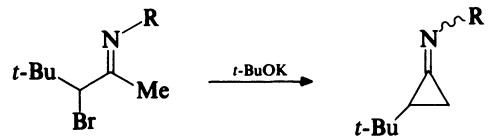


(9) (10) (11)

SCHEME 4



(13) (12) (5)



(14) (6)

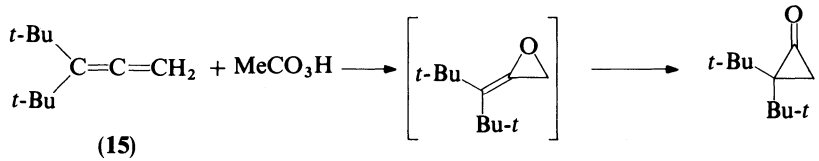
products exist as mixtures of (*E*,*Z*) diastereomers. The (*E*)/(*Z*) ratio of the diastereomers increases with the increasing size of the substituent on nitrogen[34].

In neutral as well as in basic media the imines are hydrolyzed to yield the acyclic amides derived from the more highly branched carboxylic acids, paralleling the cyclopropanone ring-opening observed in the related Favorskii process.

D. The Allene Oxide–Cyclopropanone Rearrangement

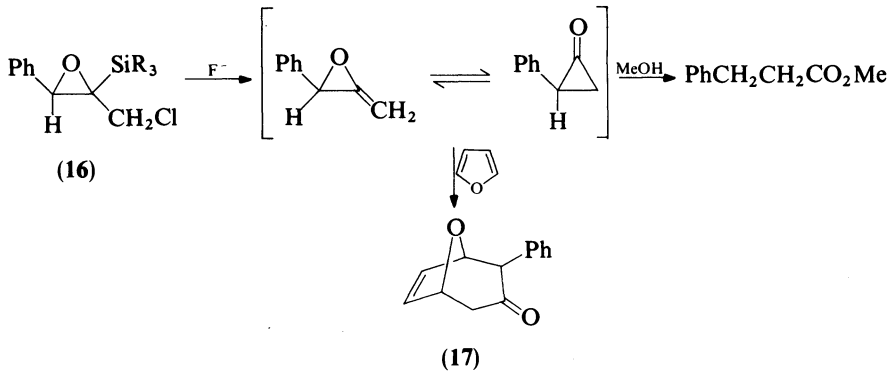
An interesting route to the cyclopropanone system involves the rearrangement of allene oxides, usually generated by the epoxidation of allenes[35]. Thus, 1,3-di-*t*-butylallene oxide (**11**) may be prepared by the reaction of 1,3-di-*t*-butylallene with *m*-chloroperbenzoic acid. Heating **11** to 100 °C leads to isomerization, forming *trans*-2,3-di-*t*-butylcyclopropanone (**10**) (Scheme 4)[31]. Similarly, 1,1-di-*t*-butylallene (**15**) yields 2,2-di-*t*-butylcyclopropanone with peracetic acid (equation 7)[36, 37].

Recently, Chan showed that the allene oxide–cyclopropanone system can be formed[38] starting with the silylated epoxide (**16**). Fluoride ion promoted elimination was carried out



(15) (7)

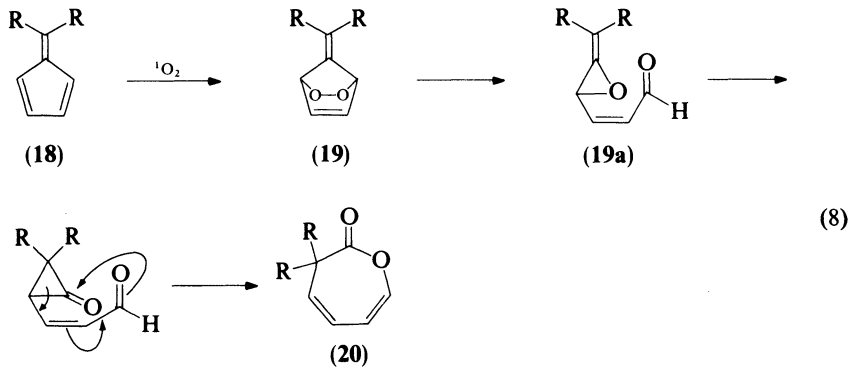
in the presence of trapping agents such as methanol and conjugated dienes. The allene oxide initially formed isomerized to the cyclopropanone, which then took part in the expected 1,4-addition to the diene. In the presence of furan, the addition product (**17**) was isolated[38]. With methanol, methyl β-phenylpropionate was formed, apparently by a standard cyclopropanone ring-opening (Scheme 5).



(16) (17)

SCHEME 5

An unusual example of the allene oxide–cyclopropanone isomerization is found in the results of singlet oxygen oxygenation of 6,6-disubstituted fulvenes (**18**)[39, 40]. The production of 3,3-disubstituted 2(3*H*)-oxepinones (**20**) in this process can be rationalized by the sequence of transformations outlined in equation 8. The initially formed endoperoxide (**19**) undergoes a well-precedented rearrangement to the epoxy ketone (**19a**) which contains the allene oxide residue. Rearrangement to the cyclopropanone form is



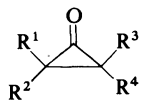
(18) (19) (19a) (20) (8)

then followed by attack of the carbonyl oxygen on the adjacent electrophilic cyclopropanone carbonyl group leading to ring-opening and oxepinone formation.

III. PHYSICAL PROPERTIES OF CYCLOPROPANONES

Very few cyclopropanones have been isolated in the pure state, and a study of their properties has therefore depended on examination of their spectroscopic behavior in solution. The infrared spectra of cyclopropanones are characterized by a carbonyl stretching vibration of unusually high frequency and this has been used as a method of detection. Table 3[41] shows the IR bands of cyclopropanone and a number of substituted derivatives. The carbonyl absorption in each of these systems, (1813–1825 cm^{-1}) reflects the strain in the ring. This band appears as a doublet in some cases as a consequence of the accidental degeneracy of an overtone of another low lying vibration mode (Fermi resonance)[42–44]. The shift to high frequency in both CO and CH stretching of cyclopropanones may be associated with a strain-induced rehybridization of the ring bonds associated with a decrease in ring size. As a consequence, the p character of the ring bonds increases with an accompanying increase in the s character of the exocyclic bonds and therefore an increase in the CO and CH bond strengths.

TABLE 3. IR bands of cyclopropanones[41]

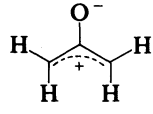


Compound	Solvent	Bands (cm^{-1})	Ref.
	CH_2Cl_2	3045 (C–H) 1813 (C=O)	5, 11
$R^1 = R^2 = R^3 = R^4 = H$	CCl_4	1816 (C=O)	6
	$CHCl_3$	1908, 1822 (C=O)	43
R^1 = Me, $R^2 = R^3 = R^4 = H$	CH_2Cl_2	1850, 1822 (C=O)[42–44]	11
$R^1 = R^2$ = Me, $R^3 = R^4 = H$	CH_2Cl_2	3050 (C–H) 1815 (C=O) 1387–1380 (d, $C(Me)_2$ bending)	11
$R^1 = R^2 = R^3 = R^4$ = Me	CH_2Cl_2	1843, 1823 (C=O)[42–44]	11
$R^1 = R^3 = R^4$ = Me, $R^2 = H$	CH_2Cl_2	1822 (C=O) 1387, 1380 ($C(Me)_2$ bending)	95
$R^1 = R^2$ = *t*-Bu, $R^3 = R^4 = H$	CH_2Cl_2	1825 (C=O)	36
$R^1 = R^4$ = *t*-Bu, $R^2 = R^3 = H$	CCl_4	1822 (C=O)	8

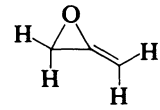
A. Microwave Spectra

Important structural information can be derived by an analysis of the microwave spectra of cyclopropanone along with the isotopic isomers $^{13}C(1)$–$^{13}C(2)$ and 2,2-dideuteriocyclopropanone[45]. The rotational transitions were determined by an analysis of the Stark effect (the shifts and splittings of lines produced by an electric field) and the type of transition observed for cyclopropanone is considered to be consistent with C_{2v} symmetry. The sum of

the moments of inertia ($I_a + I_b + I_c$) indicate that all four protons are out-of-plane. This helps to rule out structural alternatives such as the dipolar oxyallyl tautomer (**21**) and



(**21**)

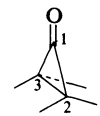


(**22**)

allene oxide (**22**). The electric dipole moment (μ_a) was calculated to be 2.67 ± 0.10 D, corresponding to an average of the moments of acetone (2.93 D)[46] and formaldehyde (2.34 D)[47].

Study of the microwave spectra also provides a precise description of the bond lengths and angles (Table 4). The C(2)–C(3) bond is unusually long and relatively weak as confirmed by the reactivity of substituted cyclopropanones in cycloaddition reactions. The carbon–oxygen bond is somewhat shorter than that found in the average carbonyl group as reflected in the IR spectra of cyclopropanones outlined above.

TABLE 4. Bond distances and bond angles of cyclopropanones[41]



	Cyclopropanone[63]	Model[a]
Bond distances (Å)		
C(1)–O	1.191 ± 0.020 Å	1.23 ± 0.03, acetone
C(1)–C(2)	1.475 ± 0.017 Å	1.52 ± 0.03, acetone
C(2)–C(3)	1.575 ± 0.012 Å	1.53 ± 0.01, cyclopropane
C(2)–H	1.086 ± 0.025 Å	1.09 (assumed) acetone
Bond angles		
C(1)–C(2)–C(3)	$57°42' \pm 25'$	
C(2)–C(1)–C(3)	$64°36' \pm 50'$	$93°1' \pm 0.3°$, cyclobutanone[b]
HCH plane angle with C(2)–C(3) axis	$29°7' \pm 2°$	
HCH	$114°8' \pm 2°$	

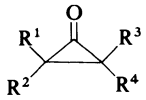
[a] *Tables of Interatomic Distances and Configuration in Molecules and Ions*, London, Chemical Society, 1958.
[b] L. H. Scharpen and V. W. Laurie, *J. Chem. Phys.*, **49**, 221 (1968).

B. Electronic Absorption Spectra (UV and ORD)

In cyclopropanone, the $n \rightarrow \pi^*$ transition occurs at 310 nm ($\varepsilon = 23$) (compared to 280 nm ($\varepsilon = 15$) for simple ketones)[48]. With successive alkylation of the α-carbons, a shift to longer wavelengths takes place (Table 5). The longer wavelength of this transition in cyclopropanones has been attributed to a strain-induced destabilization of the ground state and a favorable charge situation in the excited state[3].

Optically active *trans*-2,3-di-*t*-butylcyclopropanone has been prepared by asymmetric destruction of the racemic compound using *d*-amphetamine[49]. The (+)-cyclopropanone,

TABLE 5. n → π* Transitions in cyclopropanones[41]



Compound	Solvent	λ_{max} (nm)	ε, (M^{-1} cm^{-1})	Ref.
$R^1 = R^2 = R^3 = R^4 = H$	CH_2Cl_2	310	23	5
		330 (sh)	15	
$R^1 = R^3 = R^4 = H$, $R^2 = Me$	CH_2Cl_2	330	18	11
$R^1 = R^2 = Me$, $R^3 = R^4 = H$	CH_2Cl_2	340	27	11
$R^1 = R^2 = R^3 = R^4 = Me$	CH_2Cl_2	340 (350)	20	11
$R^1 = R^2 = t$-Bu, $R^3 = R^4 = H$	Hexane	345	52	36
$R^1 = R^4 = H$, $R^2 = R^3 = t$-Bu	Isooctane	354	33	8

$[\alpha]_{436} + 76\,°C$ (C = 0.5, CCl_4) exhibits a positive Cotton effect with a peak at 370 nm, and undergoes racemization on heating.

C. Nuclear Magnetic Resonance Spectra

The protons of cyclopropanones show signals shifted upfield from those in unstrained ketones in the range 1.1–2.1 ppm (Table 6). This is understandable in terms of the presence of a shielding field associated with the cyclopropane ring[50]. ^{13}C-coupling constants have also been measured for the ring protons of 2,2-dimethylcyclopropanone. The splitting ($J(^{13}CH) = 160$ Hz)[11] is the same as that found in cyclopropane (161 Hz)[51].

One may use NMR to observe the dynamic equilibrium between cyclopropanone and certain hemiketals and related derivatives. While the ring protons of 1-acetoxycyclopropanol exhibit an A_2B_2 pattern, indicating a slow interconversion with the ketone, they appear as a sharp singlet in the methyl and ethyl hemiketals, in accord with a rapid equilibration with cyclopropanone[11, 19a]. Other cases indicate that the interconversion process is base-inhibited[16] and requires, as substituents at the 1-position, a good leaving group and a heteroatom capable of multiple bonding[52, 53].

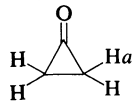
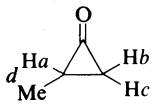
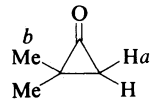
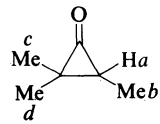
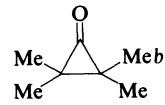
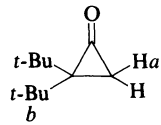
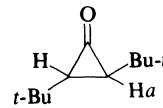
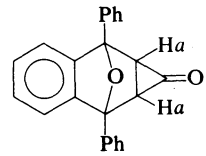
IV. THEORETICAL STUDIES

Because of its unique structure and bonding characteristics, cyclopropanone has been the subject of a number of theoretical calculations carried out to various levels of approximation[54–64]. These have dealt with the structure[54], reaction paths[61] and rearrangements of this strained cyclic ketone[62, 63].

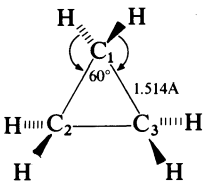
Fujimoto and coworkers[64] studied the molecular structure of cyclopropanone considering the orbital interaction between the ethylenic part and the C=O part of the molecule, as shown in Figure 1. They pointed out that the high-lying antibonding MO of the C=O bond favors a greater contribution of π* from CH_2CH_2, resulting in an extraordinarily long carbon–carbon distance between the two methylene groups.

Microwave and Raman studies on cyclopropane (**23**)[65], cyclopropanone (**24**)[45] and methylenecyclopropane (**25**)[66] show that the oxygen and methylene substituents both

TABLE 6. NMR data for cyclopropanones[41]

Compound	Solvent	δ ppm (TMS) Ha	Hb	Hc	Hd	Ref.
	CH_2Cl_2 Neat or $CFCl_3$	1.65(s) 1.72(s)				11 6
	CH_2Cl_2	{1.85–2.1 (m, 1 H) 0.9–1.8 (m, 4 H)}				11
	CH_2Cl_2	1.20(s)	1.40(s)			11
	CH_2Cl_2	1.1–1.4(m)	1.22(d, J_{ab} = 5)	1.12(s)	1.36(s)	95
	CH_2Cl_2		1.19(s)			11
	CH_2Cl_2	1.44(s)	1.10(s)			36
	CCl_4	1.55(s)	0.96(s)			8
	CCl_4	2.75(s, $J_{^{13}CH}$ = 173; J_{HH} = 9.0)				79

* *c,d.* assignments are arbitrary and may be reversed.



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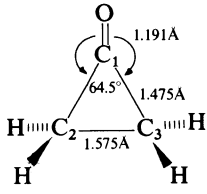
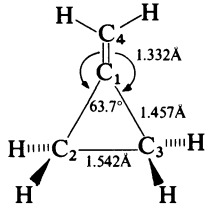


(24)



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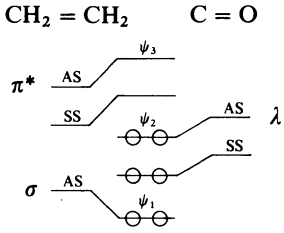


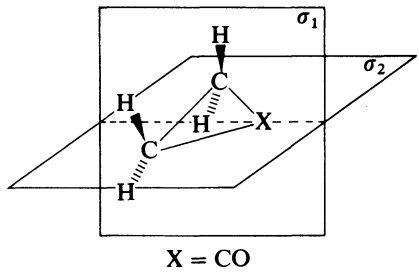
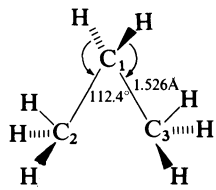


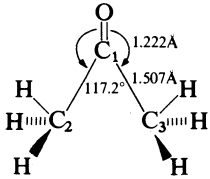
FIGURE 1. Illustration of orbital interaction between the fragments of cyclopropanone

serve to shorten the adjacent bonds (C(1)–C(2) and C(1)–C(3)) and lengthen the opposite bond (C(2)–C(3)) in the ring. The oxygen substituent shortens the adjacent bond less and lengthens the opposite bond more.

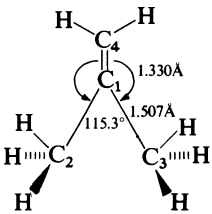
Microwave studies on propane (**26**)[67], acetone (**27**)[68–70] and isobutylene (**28**)[71] reveal that ring formation results in a shortening of the C=O bond leaving the C=C bond unaffected.



(26)



(27)



(28)

In order to elucidate the origin of these substituent and ring-closure effects, Allen and coworkers carried out *ab initio* calculations on the molecules **23**–**28**[72]. It was concluded that the interaction between oxygen and methylene with MO 3 of cyclopropane, as shown in Figure 2, strengthens the adjacent (C(1)–C(2,3)) bonds by removing the antibonding overlap in this cyclopropane orbital and helping to direct the charge density more effectively along the C(1)–C(2,3) bond axes. These two effects result in a shortening of the adjacent bonds. On the other hand, the oxygen MO 9 and methylene MO 9 interactions generate a charge decrease on C(1) and a charge increase on C(2) and C(3) in MO 9. This charge redistribution reduces the bonding overlap between C(1)–C(2,3) and increases the antibonding interaction between C(2)–C(3) (Figure 2) leading to a lengthening of the

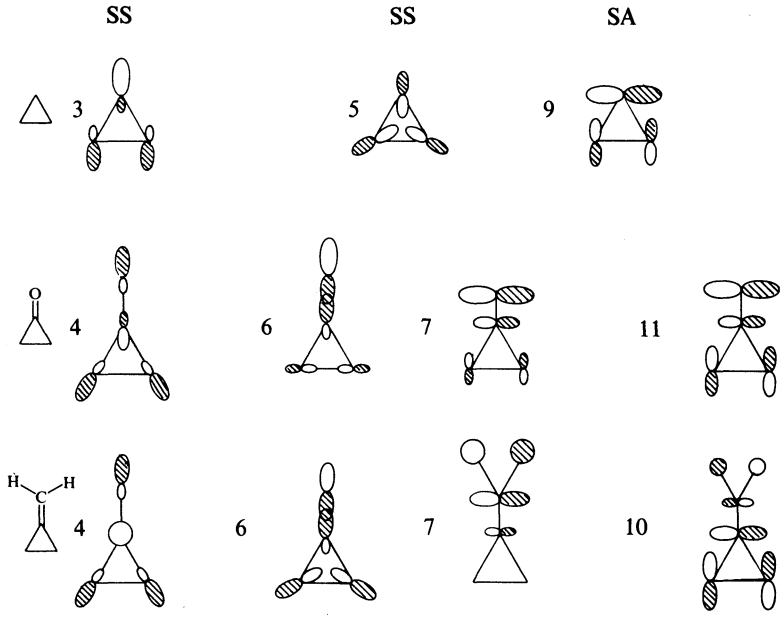


FIGURE 2. Molecular orbital diagrams for carbonyl and methylene addition to cyclopropane. This orbitals are classified according to the reflections in the plane of the molecule and perpendicular to it (SS, SS, SA). Related orbitals of a given type are shown vertically under the symmetry heading

C(1)–C(2), C(1)–C(3) and C(2)–C(3) bonds. The CH_2 bonding orbital of SA symmetry is more stable than the corresponding oxygen orbital since the latter is a lone pair, whereas the CH_2 orbital is delocalized over all three atoms. As a result, the oxygen substituent interacts more effectively with the cyclopropane orbital of SA symmetry. The stronger substituent–parent molecule interaction for O relative to CH_2 is responsible for the differential bond (C(1)–C(2,3)) shortening and bond (C(2)–C(3)) lengthening in cyclopropanone and methylenecyclopropane.

The above considerations serve to explain why the C=O bond is shortened while the C=C bond distance remains unaffected upon ring-closure of acetone and isobutylene to cyclopropanone and methylenecyclopropane, as shown in Figure 3.

In studies on the photodissociation of cyclopropanone, Yamabe and coworkers performed *ab initio* calculations to explore the minimum-energy modes of symmetry-allowed reaction pathways[61]. They found that the activation energy is too high to permit facile thermal dissociation in the ground state to form CO and C_2H_4. (Thermolysis of cyclopropanone yields only polymerized product[44].) It was noted that there are two crossing points of the ground state ($^1S_0$) and the first excited state ($^{1,3}A$) potential energy curves as shown in Figure 4. It was suggested that the dissociation is initiated predominantly from the lowest excited state, taking the bent-in-plane path to form the biradical intermediate, as indicated by the energy minimum at the energy curve ($R \sim 1.8$ Å). At the left crossing point ($R \simeq 1.6$ Å) there is the probability of internal conversion or intersystem crossing ($^{1,3}A \rightarrow {}^1S_0$) back to the unreactive electronically ground (but vibrationally excited) state of cyclopropanone. When the reaction is advanced further to the right crossing point ($R \sim 1.9$ Å), it is transferred to a dissociative part of the

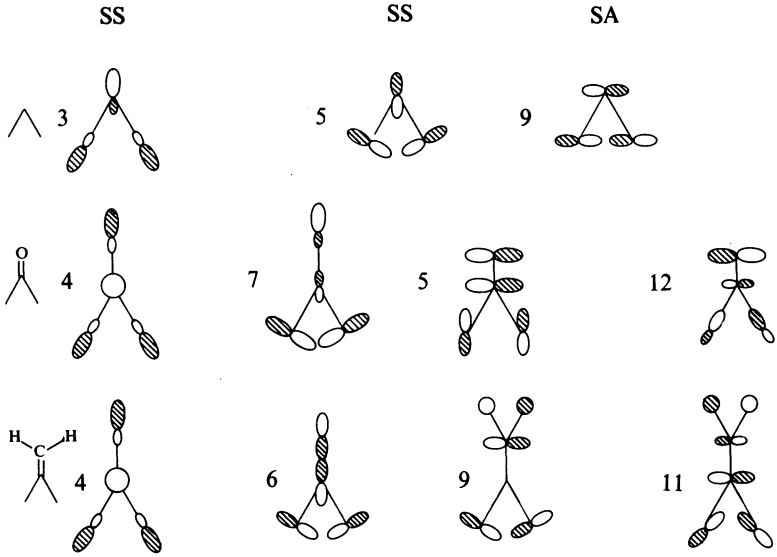


FIGURE 3. Molecular orbital diagrams for carbonyl and methylene addition to propane. The orbitals are classified according to the reflections in the plane of the molecule and perpendicular to it (SS, SS, SA). Related orbitals of a given type are shown vertically under the symmetry heading

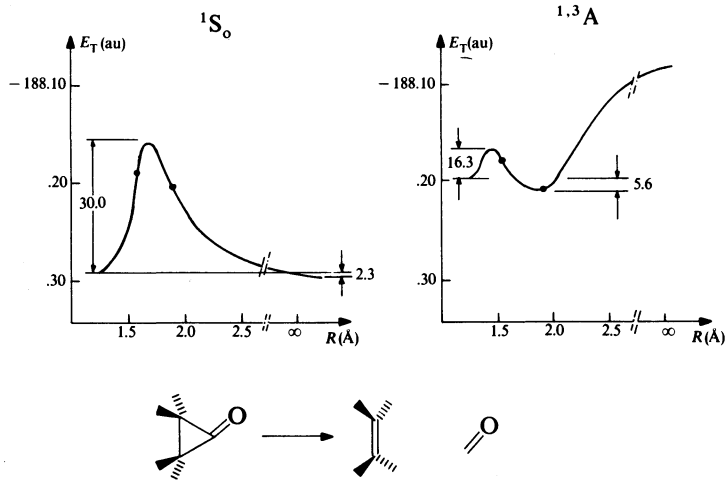
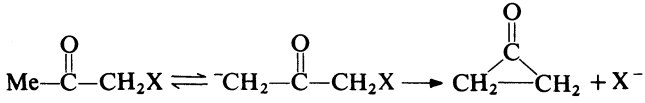


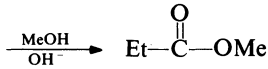
FIGURE 4. The energy curves corresponding to the two bent-in-plane paths for the photodissociation of cyclopropanone

ground-state surface to yield the ground state CO and C_2H_4. This result supports the mechanism proposed by Thomas[44].

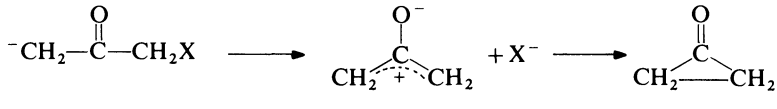
Cyclopropanone is a generally accepted intermediate in the Favorskii rearrangement, as shown in equation 9[14]. Bordwell[73] has suggested that the second step of the Favorskii



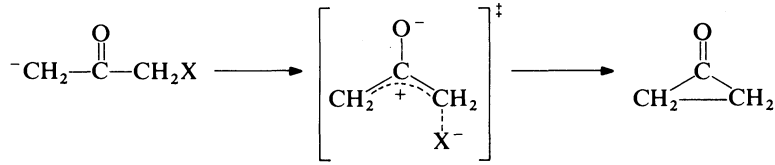
(29) (30) (24) (9)



rearrangement is an S_N1-type reaction producing a dipolar intermediate, **21** (oxyallyl), which subsequently undergoes a disrotatory ring-closure to **24** (equation 10). However, his experiments do not rule out a direct conversion of **30** to **24** through a transition state **31** (equation 11).



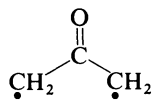
(30) (21) (24) (10)



(30) (31) (24) (11)

In order to determine which path is operative in the Favorskii rearrangement, Schaad and Hess carried out single-configuration SCF calculations using Pople's 4-31G Gaussian basis on cyclopropanone and on oxyallyl[63]. It was found that there is no barrier to the disrotatory ring-closure of the oxyallyl fragment to cyclopropanone. Consequently, the path of equation 10 is ruled out for the rearrangement, but it may be a point on the reaction pathway. However, the electronic state for oxyallyl varies with different basis sets and therefore is not best described by a single-configuration wave function[58,74,75].

A recent higher level calculation by Osamura and coworkers[74] on oxyallyl with MCSCF/3-21G and MCSCF/3-21G* wave functions led to the conclusion that the ground state is $^3B_2$ but the first excited state is $^1A_1$, which is only 6 kcal mol^{-1} higher in energy[76]. The $^1A_1$ state is best described as a diradical (**32**) rather than a zwitterion (**21**), with a strong C–O π bond and an electron largely localized at each of the peripheral carbon atoms. Based on the analysis of the vibrational frequencies of $^1A_1$, they suggested that oxyallyl is a true intermediate of the ring-opening of cyclopropanone. Other recent studies have included an evaluation of the kinematic and potential energy contributions to the

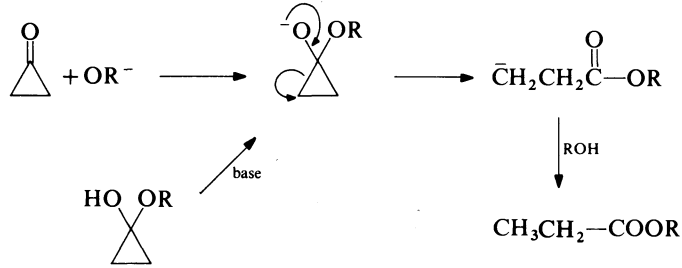


(32)

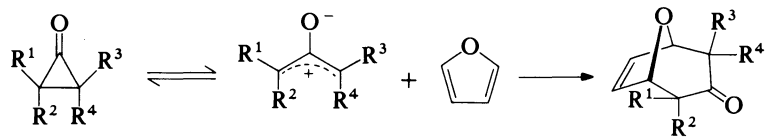
C=O frequency changes of cyclopropanone[77], as well as an electron density analysis of the parent ketone[78].

V. REACTIONS OF CYCLOPROPANONES

Cyclopropanones undergo reaction in varied ways. On thermolysis, they may take part in decarbonylation[49,79], polymerization[6,11] or ring-opening[5,7,80]. In photochemical reactions, decarbonylation and polymerization have been observed[11,81]. All of the bonds in the cyclopropanone are labile, and one may observe either 1,2- or 2,3-bond breakage in the ring-opening reaction. Ring-opening resulting from carbonyl attack is the more common cleavage observed, and this accounts for much of the chemistry of the cyclopropanone molecule. In practice, attack of a nucleophilic reagent at the site of the carbonyl generates a 1,1-disubstituted addition product which then may suffer cleavage under the influence of acid or base. Alternatively, the ring-opening may take place as part of a ring-expansion process, particularly if a cyclopropyl carbinyl cation or cyclopropyl nitrenium ion can be formed. This reaction then may lead to cyclobutanone or β-lactam products. As noted earlier, a very common example of the ring-opening of cyclopropanone intermediates is found in the second step of the Favorskii reaction (Scheme 6). It has been calculated that approximately 78 kcal mol^{-1} are required for the isomerization of the cyclopropyl system to the oxyallyl tautomer[55]. With successive alkyl substitution at the site of the C(2) and C(3) carbon atoms, this value decreases significantly[82]. For example, in the case of *trans*-2,3-di-*t*-butylcyclopropanone, it was estimated that the cleavage of the C(2)–C(3) bond requires only about 27 kcal mol^{-1} [49]. Examples of the use of this type of ring cleavage is found in the 4 + 3 → 7 cycloadditions observed in the reaction of cyclopropanones with 1,3-dienes[83], as illustrated in Scheme 7.



SCHEME 6



SCHEME 7

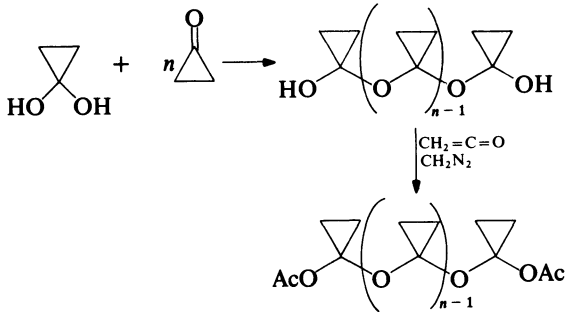
A. Additions to the Carbonyl Group

1. Polymerization

As mentioned earlier, many types of nucleophilic reagents will add to the carbonyl group of cyclopropanones, including water, alcohols, amines and Grignard reagents. This type of reaction is most probably involved in the ready polymerization observed in these systems. For example, cyclopropanone forms a polymer, polycyclopropanone (**33**), when warmed

(**33**)

above 0°C in the absence of any inhibitor or stabilizing nucleophilic species[5,6,84]. The polymer is a white solid, the molecular weight of which has variously been reported as 3000[11] to 9500[6]. The NMR spectrum of this product contains a broad singlet at 1 ppm and IR bands at 1450, 1310, 1130, 1010, 975 and 950 cm^{-1} [6]. This polymerization (equation 12) is initiated by traces of water[85] and inhibited[86] by scavengers of moisture, such as acetyl chloride. The terminal groups seem to be hemiketal units, since α,ω-diacetoxy-poly(oxycyclopropylidines) (**34**) are isolated from the mixture of cyclopropanone hydrate, diazomethane and excess ketene[85].



(12)

(**34**)

2. Addition of water, alcohols and acids

Cyclopropanones readily take up water, alcohols and carboxylic acids to form the corresponding hydrate, hemiketal or 1-acetoxy carbinols. The hydrates are relatively stable, but the hemiketals appear to be in equilibrium with the parent ketone, as evidenced by the fact that one hemiketal may be converted to another on standing with the appropriate alcohol[19a]. The formation and reactions of these cyclopropanone hemiacetals is reviewed in the chapter by Salaun[1] (cf. Chapter 13) and will not be covered extensively here.

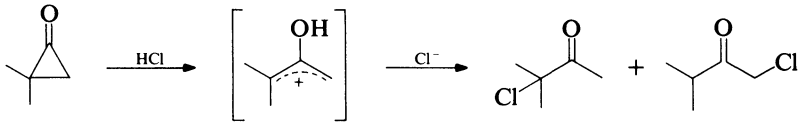
In other additions, cyclopropanone forms an addition product with HCN[84] which can be hydrolyzed to form the hydroxy acid **35** (equation 13)[87]. The latter is unusually stable to acid. With HCl, cyclopropanone affords the chlorohydrin **36** (equation 14), but the 2,2-dimethyl derivative undergoes ready ring-opening to form a mixture of **37** and **38**, as might be expected from the opportunity to form the more stable dimethylhydroxyallyl cation (equation 15).

(13)

(35)

(14)

(36)

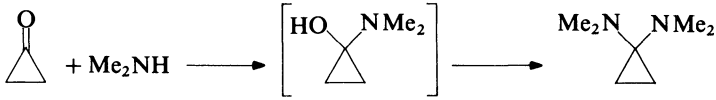


(15)

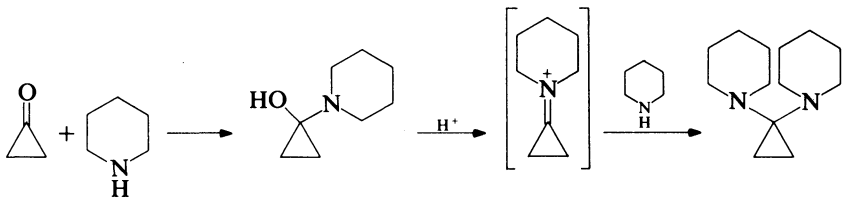
(37) (38)

3. *Reactions with amines*

The addition of ammonia and amines to cyclopropanone provides carbinol amines which may undergo further reaction to form more complex products, as shown in Scheme 8. In some cases, the initially formed carbinol amines may be isolated, as in the case of 1-piperidino and 1-morpholino cyclopropanol[52]. The further reaction of these derivatives appears to take place through cyclopropyl iminium salts (Scheme 9). The nature of the product formed in these imine addition reactions depends significantly on the reaction conditions. Thus, with cyclopropanone and excess aniline at low temperature, the simple addition product is formed almost quantitatively[19a]. However, at 25°C, both monoanilino and the dianilino derivatives are formed (equation 16)[19a].

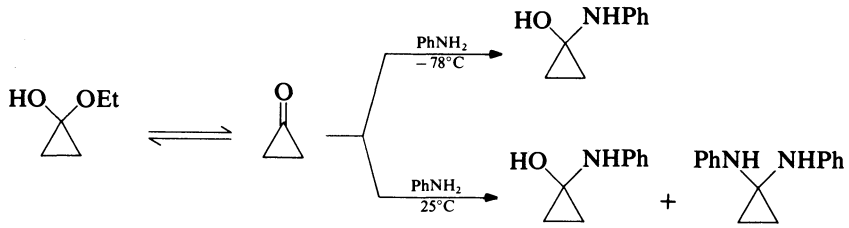


SCHEME 8



SCHEME 9

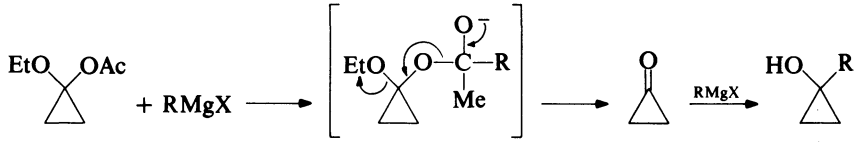
The addition of amino acids to cyclopropanones through hemiketal intermediates provides a means of obtaining carbinol amines which may be converted to β-lactams, as outlined in a later section.



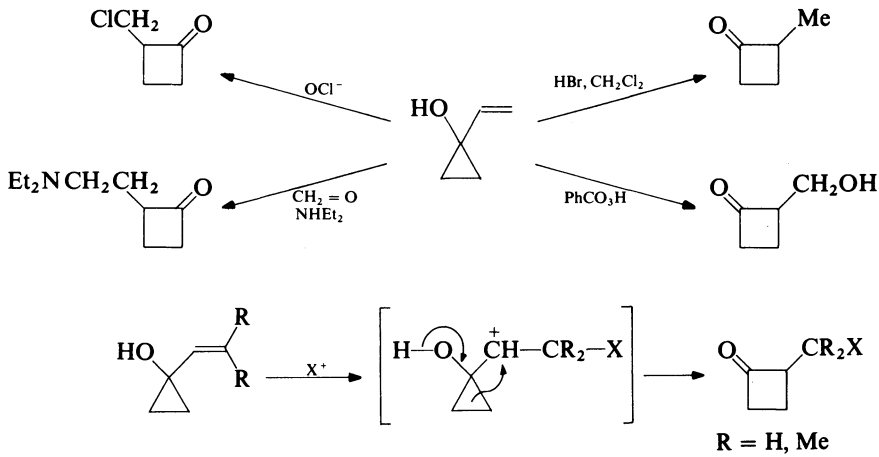
(16)

4. *Other carbonyl addition reactions*

Cyclopropanones will react with Grignard reagents to give 1-substituted cyclopropanols. In practice, this reaction may take place either with the hemiketal or with other derivatives capable of generating cyclopropanone *in situ*[19a, 88]. Thus, 1-ethoxycyclopropyl acetate reacts with 2 moles of Grignard reagent to give the 1-substituted alcohol. The first mole of reagent is used to generate the free cyclopropanone. A wide variety of such reagents have been used as nucleophiles, including the vinyl Grignard reagent as shown in the reaction with the ethyl hemiketal[82] (equation 17). Formation of vinylcyclopropane derivatives by this process provides precursors for ring enlargement to cyclobutanones through the cyclopropyl carbinyl cation as shown in Scheme 10[89].



(17)

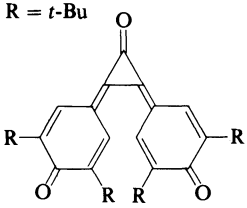
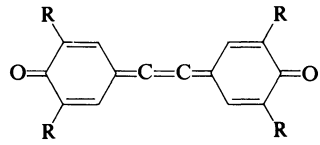
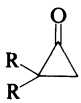
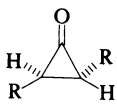
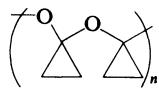
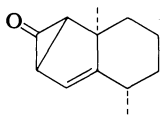
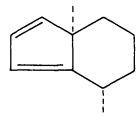
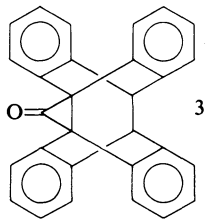
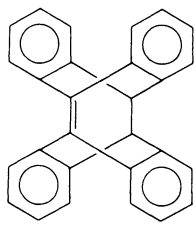
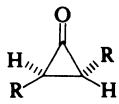


SCHEME 10

B. Decarbonylation

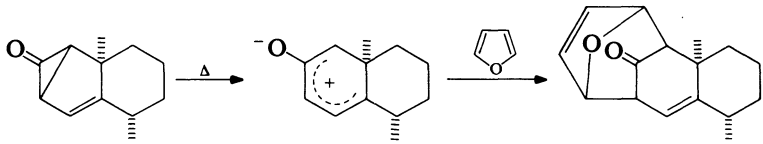
Loss of carbon monoxide from cyclopropanones may take place under thermal or photochemical conditions to generate the corresponding unsaturated product. In Table 7 are listed a number of cyclopropanones along with the conditions and the products formed on loss of carbon monoxide.

TABLE 7. Cyclopropanone decarbonylation reactions[41]

Cyclopropanone	Conditions	Products	Ref.
Thermal R = *t*-Bu 	Room temp.		181
	600°C		36
	150°C		49
Photochemical 	Gas phase, 2920 Å 3650 Å	$H_2C{=}CH_2$ + 	81
	Neat glass, 3000–3600 Å −190°C		80
	3500 Å, benzene		179
	Sunlamp, 0°C		49

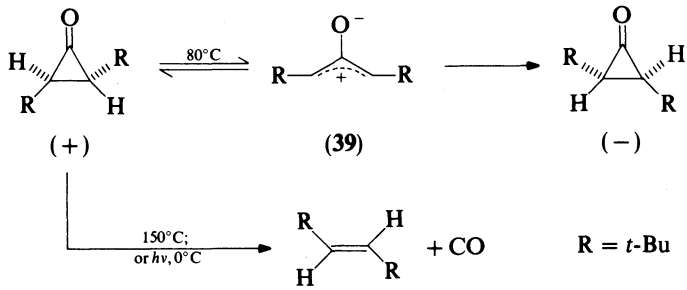
C. Ring-opening by C(2)–C(3) Bond Rupture

Another mode of reaction exhibited by cyclopropanones involves the cleavage of the C(2)–C(3) bond under thermolysis to generate the oxyallyl species. This can usually be trapped as a cycloadduct with a diene such as furan (equation 18).



(18)

Greene and coworkers have been able to observe ring-opening and decarbonylation as two distinct thermal reactions (Scheme 11) during kinetic studies on optically active *trans*-2,3-di-*t*-butylcyclopropanone[49]. The ring cleavage is measurable at 80°C in terms of the rate of recemization, while the decarbonylation is not observed until 150°C. The fact that racemization proceeds through the oxyallyl species (**39**) is supported by the observation of a first-order rate dependence and zero incorporation of solvent deuterium. The loss of CO is, of course, irreversible and the data are consistent with two pathways: a concerted elimination, or a stepwise fragmentation through a 1,3-diradical species.



SCHEME 11

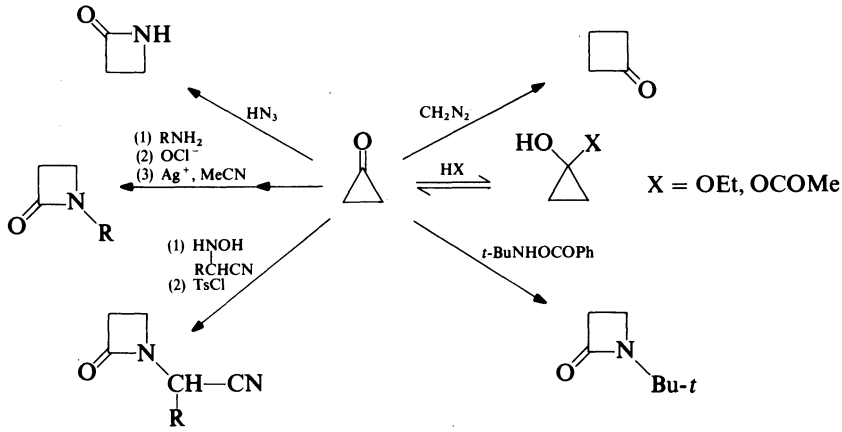
D. Ring-opening and Ring-expansion Reactions

1. β-Lactams and cyclobutanones

As noted above, reactions of cyclopropanones with nucleophiles may yield intermediates such as vinyl cyclopropanols which are readily converted to cyclobutanones through carbinyl cations[89]. In like manner, generation of electron-deficient nitrogen species may lead to the formation of β-lactams by related ring enlargement[90, 91]. Hydrazoic acid, amines and hydroxylamine derivatives have all been used in this context as shown in Scheme 12. These reactions are summarized in the examples outlined below.

(*a*) Treatment of the cyclopropanone with azide ion at pH 5.5 led to loss of nitrogen and rearrangement to the β-lactam system with varying efficiency. A particularly high yield example is found in the case of the fused ring system **40** (Table 8).

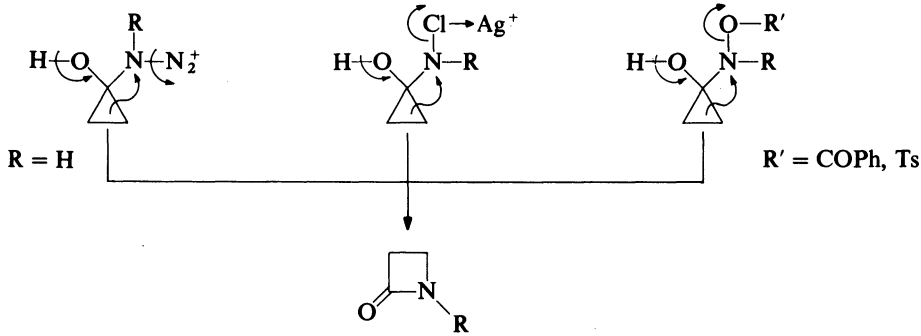
(*b*) Addition of a primary amine to a freshly prepared solution of cyclopropanone, conversion of the resulting carbinolamine to the *N*-chloro derivative, and then decomposition of this intermediate with silver ion in acetonitrile provides a sequence which



SCHEME 12

permits one to prepare *N*-substituted β-lactams of great variety (Table 8), including those constructed from amino acid esters.

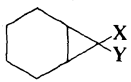
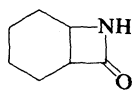
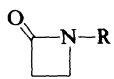
In the above sequences, the ring enlargement appears to take place through a nitrenium ion adjacent to the cyclopropyl system at the 1-position of the cyclopropanol. In the case of the azide addition, the leaving group generating the electron-deficient nitrogen is N_2; in the second case, it is halide. A further modification of the procedure permits introduction of the leaving group (tosylate) under mild conditions. Addition of a substituted hydroxylamine to the cyclopropanone precursor generates a *N*-hydroxy carbinolamine which may be converted to the nitrenium ion by treatment with TsCl (Scheme 13).

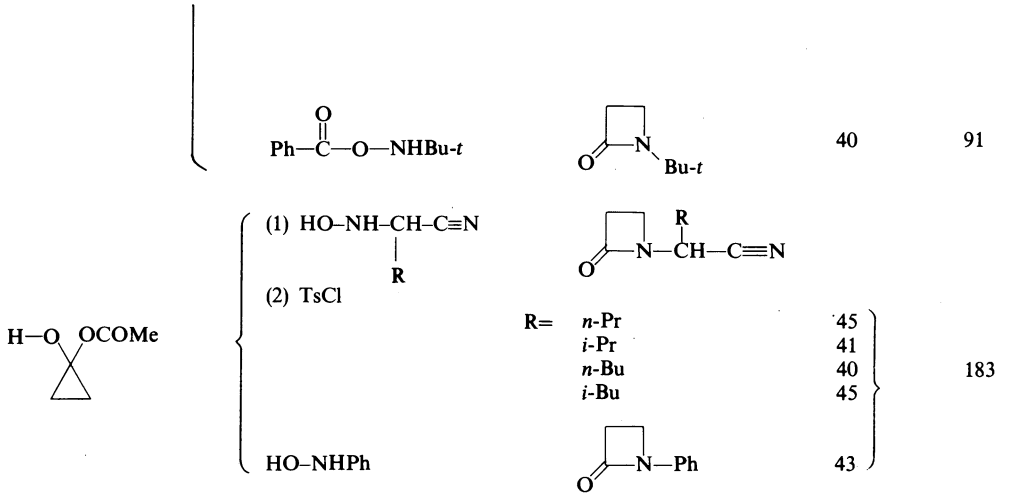


SCHEME 13

Cyclobutanones may be prepared without isolating the intermediate cyclopropanone by adding the ketene to excess diazoalkane (−78°C, 30 min)[92,93]. The intermediacy of cyclopropanones in this process has been shown by ^{14}C-labeling studies[94] and by comparison of the product distributions in the diazoalkane–ketene with the corresponding diazoalkane–cyclopropanone reactions[95]. When the cyclopropanone precursor is unsymmetrically substituted, the reaction with diazomethane leads to a mixture of cyclobutanones[95].

TABLE 8. β-lactams from cyclopropanones[41]

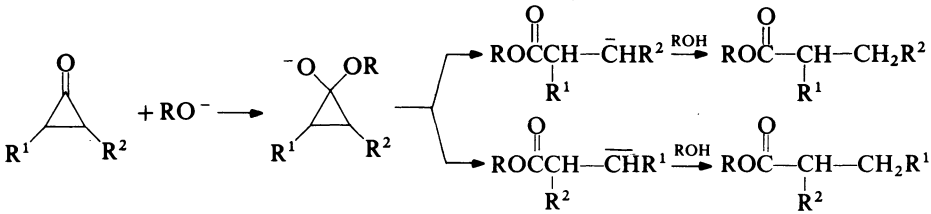
Cyclopropanone source	Nitrogen source, conditions	β-lactam	Yield (%)	Ref.
	NaN_3, pH 5.5		21	89
 (40)	X = Y = N		63	90
	X = OH; Y = N		67	
	X = OH; Y = OEt		95	
	(1) RNH_2 (2) OCl^- (3) Ag^+	 R= 	61	91
		n-Bu	43	
		sec-Bu	38	
		t-Bu	52	
		CH_2COOEt	33	182
		MeCHCOOEt	47	
		$Me_2CHCHCOOEt$	65	
		$Me_2CHCH_2CHCOOEt$	65	
		$PhCH_2CHCOOEt$	70	


Ph—C(=O)—O—NHBu-t
Bu-t
(1) HO–NH–CH(R)–C≡N
(2) TsCl
R=
n-Pr
i-Pr
n-Bu
i-Bu
H—O OCOMe
HO–NHPh
Ph
40
91
45
41
40
45
183
43

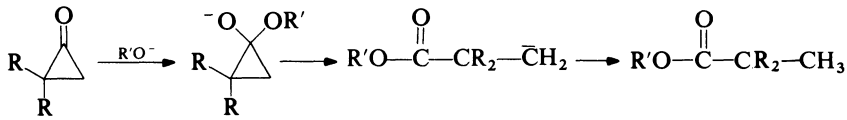
2. Ring-opening under basic conditions

Cyclopropanones may undergo ring-opening reactions under a number of different conditions. The reaction is slow in neutral media but is accelerated in acid or base. With base, the opening of the cyclopropane ring corresponds to the second stage of a standard Favorskii rearrangement (Scheme 6). The parallel nature of these two processes has been shown by labeling[30], trapping[8] and by product studies[96].

In the case of unsymmetrically substituted cyclopropanones, one would expect two possibilities for the ring cleavage, reflecting the relative stabilities of the anions formed according to Scheme 14. While this accounts for the facts in most cases, there are examples where the product distribution does not parallel the expected order of carbanion stability. Thus, in the reaction of 2,2-di-*t*-butylcyclopropanone[36], the main product is not derived from the primary carbanion but rather from the tertiary carbanion, as shown in Scheme 15. Here, the propensity of the C(1)–C(2) bond to cleave appears to be enhanced by steric considerations involving the presence of two bulky *t*-butyl substituents at C(2)[96].



SCHEME 14



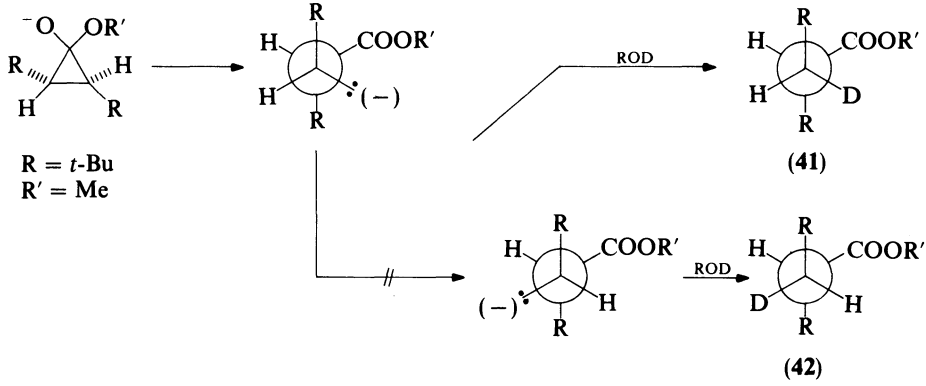
R = *t*-Bu

SCHEME 15

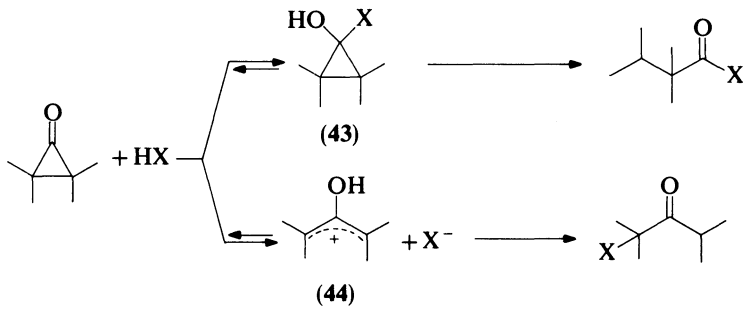
Studies on the ring-opening of *trans*-2,3-di-*t*-butylcyclopropanone with sodium methoxide or ethylene glyoxylate show that the *threo* ester (**41**) is formed exclusively with none of the *erythro* product (**42**) observed (Scheme 16). This suggests that the ring-opening under basic conditions may take place with retention of configuration[97].

3. Ring-opening under neutral and acidic conditions

Cyclopropanones and their precursors such as hemiketals undergo ring-opening of the C(2)–C(3) and/or C(1)–C(2) bond(s) forming propionate derivatives. This process is slow in neutral media but is accelerated under mildly acidic conditions. As shown in Scheme 17, the choice of cleavage site depends on the relative stabilities of the cyclopropanone-HX adduct (**43**) compared to the hydroxyallyl cation (**44**). In general, cleavage of the C(2)–C(3) bond is favored when the ring carbons contain electron-donating substituents favoring stabilization of the hydroxyallyl cation.



SCHEME 16



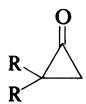
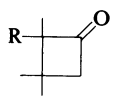
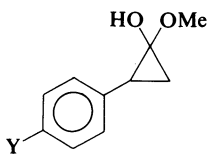
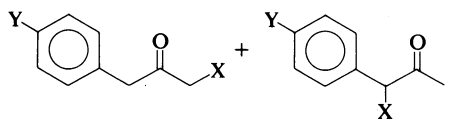
SCHEME 17

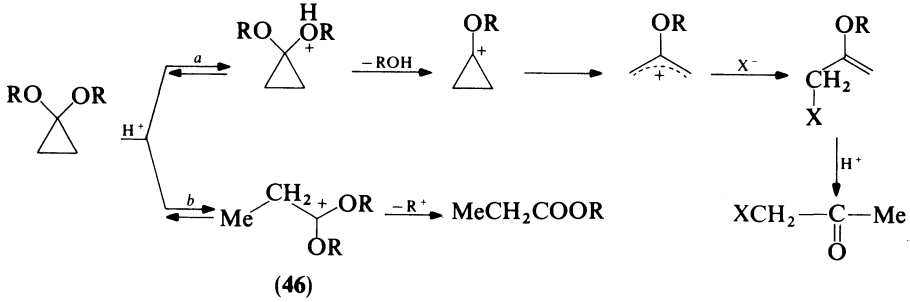
Table 9 lists cleavage products observed under different conditions for several cyclopropanones and their hemiketals. 1-Methoxy-2-phenylcyclopropanol[98], 2,2-dimethylcyclopropanone[99,100] and 2,2-di-*t*-butylcyclopropanone[36] yield ketonic products exclusively, suggesting the presence of favorable substituent interactions in the allyl cation. On the other hand, under neutral conditions, C(1)–C(2) and C(2)–C(3) cleavages are competitive in the case of tetramethylcyclopropanone hemiketals. In the absence of acid, conversion to the ketonic form is slow and 1,2-ring-opening becomes significant. In the case of the parent cyclopropanone and its hemiketals, formation of the unsubstituted hydroxyallyl cation (C(2)–C(3) cleavage) is not favored.

More vigorous conditions are required for ring cleavage of cyclopropanone ketals (concentrated acid and heat). As shown in Scheme 18, the reaction may take two pathways: (*a*) *O*-protonation, and (*b*) *C*-protonation. In the case of 1, 1-diethoxycyclopropane where both paths are competitive, refluxing hydrochloric acid yields both chloroacetone and ethyl propionate (Table 10)[100].

Giusti's studies[101] on ring-opening of a series of spiro ketal derivatives showed that, on acid hydrolysis (Table 10), ring-opening usually occurs at the site of the less-substituted carbon. The preference shown by cyclopropanone ethylene ketals for path *b* in Scheme 18 may be attributed to (i) the reversibility of path *a* due to rapid intramolecular ketalization at the incipient C(1)-carbenium ion (**45**) (R = CH_2CH_2OH) and (ii) the stability of the intermediate dioxocarbenium ion (**46**) generated in path *b*.

TABLE 9. Decomposition of cyclopropanones and cyclopropanone hemiketals under acidic and neutral conditions[41]

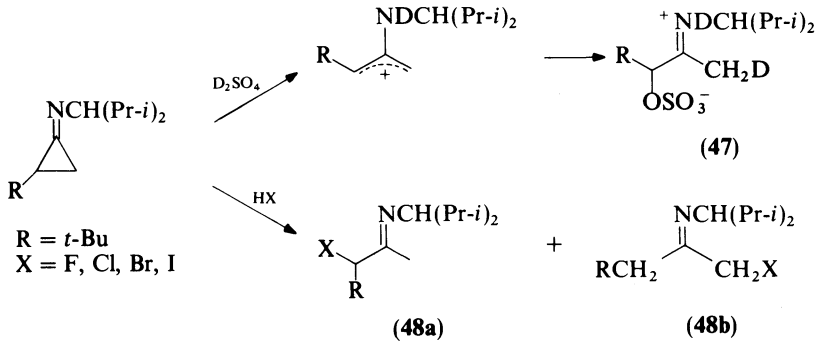
Cyclopropanone or precursor	Conditions	Products	Ref.
	Standing, or acid	EtCOOR R = H, Me, Et	7, 86
	HX	$Me_2C(X)COMe + i\text{-}PrCOCH_2X$ X = Cl, OAc	99, 184
	v.p.c.	$CH_2 = C(Me)COMe$	99
	Standing, or refluxing R'OH	$i\text{-}PrC(Me)_2COOR' + R'OC(Me)_2COPr\text{-}i$ R = Me, Et, *i*-Pr R' = Me, Et	10a, 185
	g.l.c.	$CH_2=C(Me)C(Me)_2COOR + i\text{-}PrC(Me)_2COOR + ROC(Me)_2COPr\text{-}i$ R = Et	10a
	85°C/N_2	Above products + *i*-PrCOOR + ROH R = Me	185
	Heating/O_2	Above products + MeCOMe + *t*-BuCOMe R = Me	185
	v.p.c.	$CH_2=C(Me)COPr\text{-}i$	9
	MeCOOH	 R = *t*-Bu	36
	HX	 Y = H, Cl	98



(46)

SCHEME 18

The nitrogen analogs of cyclopropanones also undergo acid-catalyzed ring-opening (Scheme 19). When the cyclopropanimine is treated with one mole of deuteriosulfuric acid in methylene chloride, C(2)–C(3) cleavage occurs affording the zwitterion **47** (90%)[33a]. However, when the acid is a hydrogen halide, both α-haloimines **48a** and **48b** are obtained with **48a** the predominating isomer in all cases.



(47)

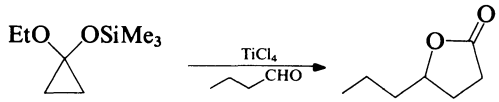
R = *t*-Bu
X = F, Cl, Br, I

(48a) **(48b)**

SCHEME 19

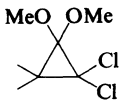
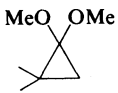
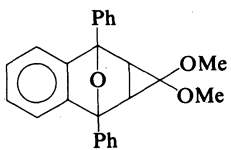
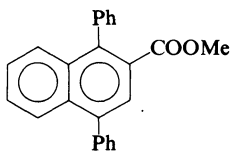
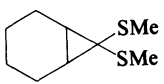
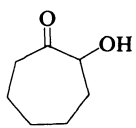
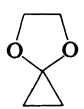
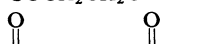
E. Cyclopropanone Derivatives as Homoenolates

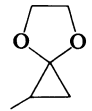
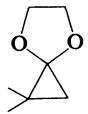
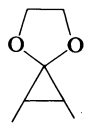
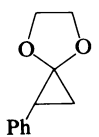
In connection with ring-opening reactions of cyclopropanol derivatives, one should note an interesting use of a cyclopropanone addition product as a homoenolate equivalent. 1-Ethoxy-1-trimethylsiloxycyclopropane, formed by reductive silylation of ethyl 3-chloropropionate, undergoes addition to carbonyl coreactants in the presence of $TiCl_4$ according to the reaction illustrated in equation 19[102]. The mechanism favored for the incorporation of the cyclopropane moiety involves $TiCl_4$-promoted ring-opening forming the equivalent of **49** which then undergoes addition to the carbonyl group (equation 20). Recently, this reaction has been explored with considerable success using zinc chloride as the Lewis acid. In this case, the ring-opening provides the equivalent of a 'homo-



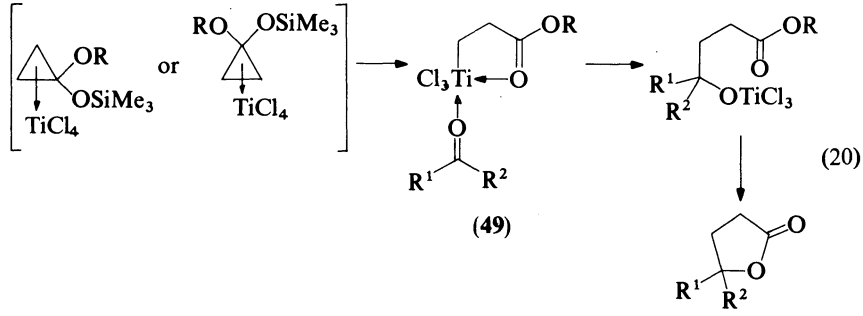
(19)

TABLE 10. Ring-opening reactions of cyclopropanone ketals under acidic conditions[41]

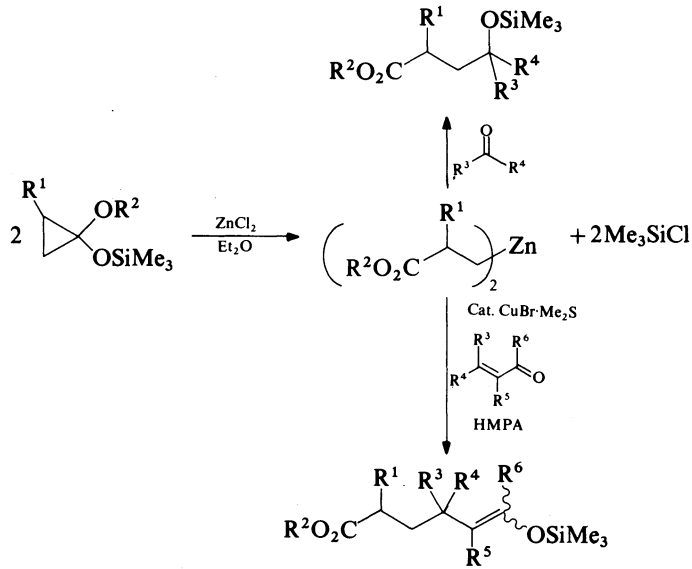
Acetal	Conditions	Products	Yield (%)	Ref.
	Conc. HCl, reflux	Et-COOEt Et-COOH	12 30	100
	Conc. HCl, reflux	$ClCH_2COMe$ $Me_2C{=}C(Cl)COOR$ R = H, Me	34 66	100
	Conc. HCl, 50 %, 1 h	$ClCMe_2COMe$	85	186
	CF_3COOH, warming			187
	HCOOH, reflux, 20–30 h		56	188
	HCl/CCl_4[a], room temp.		90	101
	Et-COOH[a], warming		83	101

	HCl/CCl_4[a], room temp.	*i*-Pr-$\overset{\overset{O}{|}}{C}$$OCH_2CH_2Cl$	93	101
	$Cl_2CHCOOH$, ether, 0°C	*i*-Pr-$\overset{\overset{O}{|}}{C}$$OCH_2CH_2O\overset{\overset{O}{|}}{C}CHCl_2$	90	101
	HCOOH/ether[a], 0°C	*t*-Bu-$\overset{\overset{O}{|}}{C}$$OCH_2CH_2O\overset{\overset{O}{|}}{C}H$	65	101
	HBr/CCl_4[a]	*sec*-Bu-$\overset{\overset{O}{|}}{C}$$OCH_2CH_2Br$	90	101
	HCl/CCl_4[a]	*sec*-Bu-$\overset{\overset{O}{|}}{C}$$OCH_2CH_2Cl$	90	101
	Et-CO_2H[a], warming	*sec*-Bu-$\overset{\overset{O}{|}}{C}$$OCH_2CH_2OCOEt$	85	101
	HCl/CCl_4[a], room temp.	$PhCH_2CH_2\overset{\overset{O}{\|}}{C}OCH_2CH_2Cl$	34	
		$Me\text{-}\underset{\underset{Ph}{\|}}{CH}\text{-}\overset{\overset{O}{\|}}{C}OCH_2CH_2Cl$	66	101

[a]Reagents are anhydrous.



Reformatsky' reagent which then adds to carbonyl derivatives according to Scheme 20. These authors also observed conjugate addition of the homoenolate anion to α,β-unsaturated ketones in the presence of copper ion as shown[102c, 103].



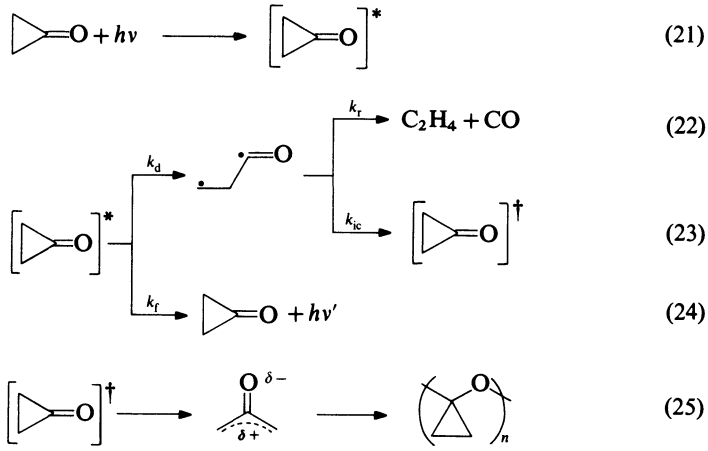
SCHEME 20

F. Thermal and Photochemical Reactions

Thomas and his coworkers have studied the gas-phase thermolysis and photolysis of cyclopropanone in detail[44]. They have found that the thermal reaction of gaseous cyclopropanone follows a first-order rate to give only the polymerized product in what appears to be a surface-catalyzed process. The heat of formation of cyclopropanone was measured to be $+3.8$ kcal mol^{-1}, and this value was used to predict an activation energy of ~ 30.5 kcal mol^{-1} for its homogeneous decomposition via the oxyallyl biradical.

It was also found that the quantum yield Φ_{cp} (~ 1.0) for decomposition of cyclopropanone was independent of the irradiation wavelength from 265 to 291 nm, whereas the yield of ethylene rose from 0.60 to ~ 1.0 as the irradiation wavelength was decreased. The

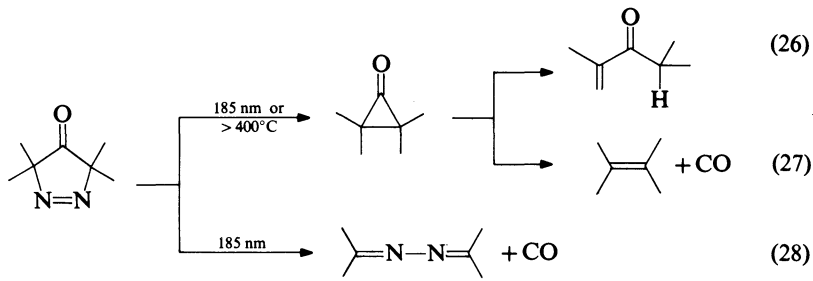
mechanism of the photodissociation of cyclopropanone, suggested by them, is shown in Scheme 21.



SCHEME 21

The dissociation to the biradical intermediate rather than intersystem crossing (ISC) for the $^1(n,\pi^*)$ state of cyclopropanone was based on the short estimated lifetime of this state. The competing processes in equations 22 and 23 accounted for the wavelength dependence of C_2H_4 formation. The rapid increase in k_r with increasing vibrational energy of the biradical which, in turn, is a function of the irradiation wavelength, resulted in the quantum yield of C_2H_4 eventually approaching 1.0 as λ_{irr} decreased to 291 nm. The k_{ic} was the rate constant in the formation of the vibrationally excited (electronically ground) state cyclopropanone via the internal conversion (IC). This 'hot' molecule then formed polycyclopropanone, presumably through the oxyallyl intermediate (equation 25).

Tetramethylcyclopropanone was found to be the intermediate in the short-wavelength (185 nm) liquid-phase photolysis and high-temperature (400–1000 °C) gas-phase pyrolysis of 3,3,5,5-tetramethylpyrazolin-4-one investigated by Quast[104, 105] as shown in Scheme 22. The major process in the 185 nm photolysis and the sole reaction in the pyrolysis of the pyrazolinone was denitrogenation, affording tetramethylcyclopropanone. The vibrationally excited cyclopropanone rearranged into α,β-enone (equation 26) or underwent decarbonylation to form tetramethylethylene (equation 27). A minor product in the

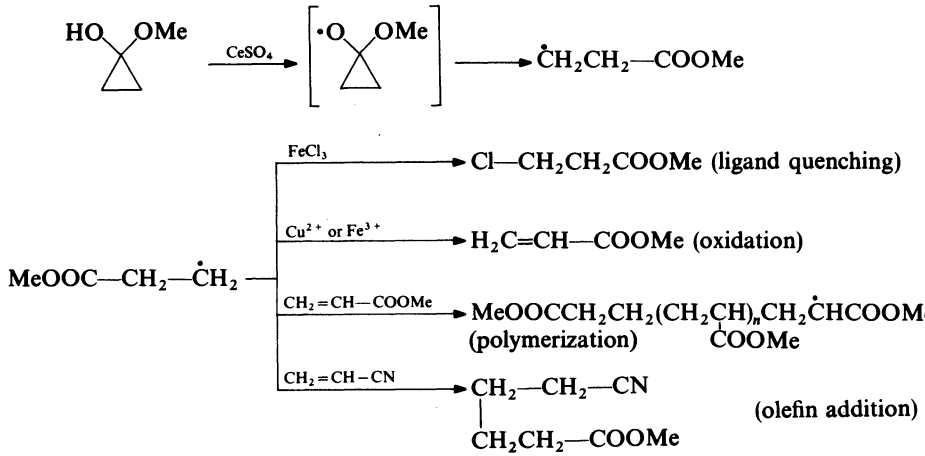


SCHEME 22

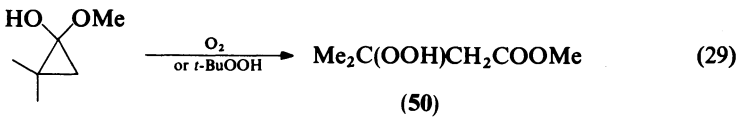
photolysis was the diazo compound (equation 28) arising from decarbonylation of the pyrazolinone.

G. Oxidative Cleavage of Cyclopropanones

Cyclopropanols and therefore cyclopropanone hemiketals are particularly sensitive to oxidative cleavage. The latter undergo oxidative cleavage of the C(1)–C(2) bond leading for the most part, to β-propionate radicals which then may undergo a variety of second-stage conversions, as summarized in Scheme 23. With air or peroxides, hydroperoxides (**50**) are formed (equation 29).



SCHEME 23



(29)

(**50**)

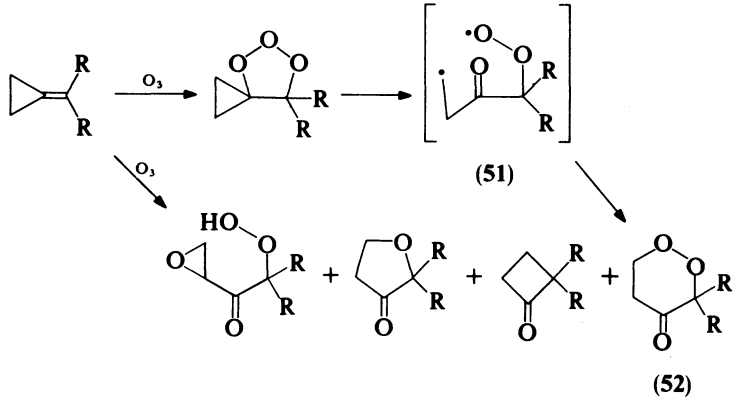
de Boer and coworkers[106–108] have studied the reactions of cyclopropylidine derivatives with ozone and singlet oxygen under a variety of conditions. These reactions, which could, in principle, yield cyclopropanone as a transient intermediate, have yielded an interesting array of products whose formation sheds light on the mechanistic processes involved. Among the products formed with ozone is **52** which appears to result from cyclization of intermediate 1,6-peroxy radical **51** (equation 30).

In the reaction of cyclopropylidene alkanes with singlet oxygen, the primary product is the hydroperoxide (**53**) (equation 31). However, in the special case of cyclopropylideneadamantane (**54**) reaction with $^1O_2$ leads to **55** by a process which most probably involves the zwitterion (**56**) (equation 32).

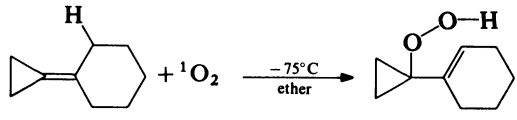
H. Cycloaddition Reactions

Cyclopropanones undergo cycloaddition reactions with 1,3-dienes ($4+3 \rightarrow 7$)[109, 110], aldehydes ($3+2 \rightarrow 5$)[111, 112] and ketenes ($2+2 \rightarrow 4$)[95, 111, 112].

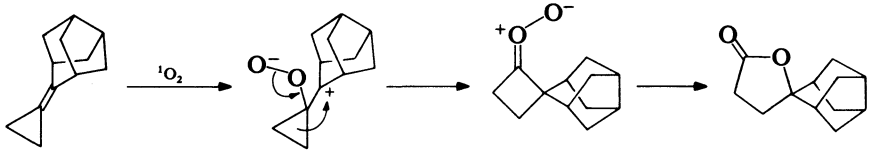
An early example of a Diels–Alder related reaction was reported by Fort who isolated the bicyclic ketone **57** from treatment of α-chlorodibenzyl ketone with 2,6-lutidine in the



(30)



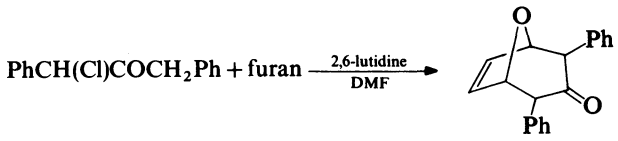
(53) (31)



(54) (56) (55)

(32)

presence of furan (equation 33)[110]. The cycloaddition of 2,2-dimethylcyclopropanone with furan and cyclopentadiene was studied by Edelson and Turro[83].



(57) (33)

VI. 1,1-DISUBSTITUTED CYCLOPROPANONE EQUIVALENTS

Some of the most important activity in connection with cyclopropanone-related chemistry during the past decade involves the reactions of cyclopropane derivatives bearing electron-attracting groups at the 1,1-position. These systems undergo ring-opening by cleavage of the C(1)–C(2) bonds paralleling the addition–ring cleavage reactions of the parent ketone, and a description of their preparation and reactions will be reviewed briefly.

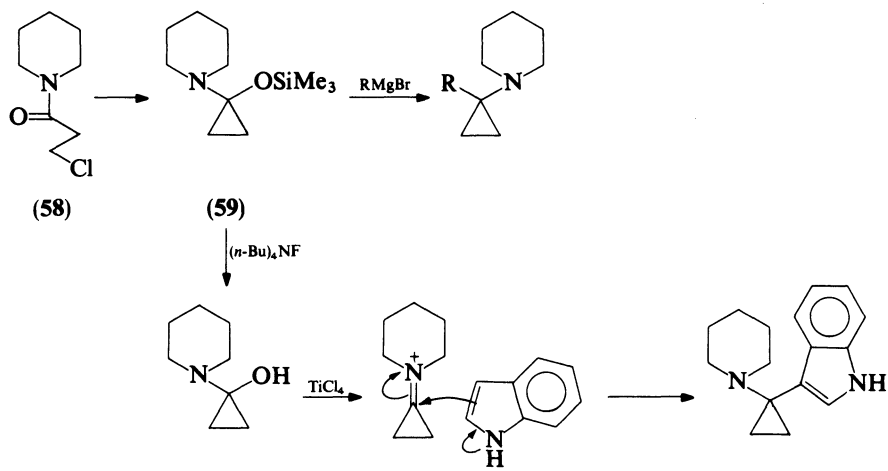
A. Carbinol Amines

Among the systems which have played the role of cyclopropanone equivalents have been cyclopropane derivatives containing both a secondary amino group and a hydroxyl substituent on the same carbon atom. These 1,1-disubstituted carbinol amines appear to be in equilibrium with the corresponding iminium salts and thereby act as reactive electrophilic sites for attack by a variety of nucleophiles.

An early preparation of these aminocyclopropanols from the hemiketals of cyclopropanone was described by Wasserman and Baird[90]. Another early description of these types of carbinol amines was provided by de Boer and coworkers who used 1-acetoxycyclopropanol as the cyclopropanone source[113].

The most recent source of these iminium ion precursors is the amide derived from 3-chloropropionyl chloride. Using the procedure reported by Ruhlmann[15] for the preparation of 1-methoxy-1-trimethylsilyloxycyclopropane, Wasserman and Dion[114a] converted the piperidide (**58**) to the 1-piperidino-1-trimethylsilyloxycyclopropane (**59**) by treatment with sodium metal in dry ether at 0 °C. This reaction, which takes place smoothly and in high yield, serves as a short, inexpensive way to form the stable cyclopropanone equivalent. Further reaction of the silyl derivative (**59**) with tetrabutylammonium fluoride in THF yields the corresponding carbinol amine (**60**).

Both the silyl derivative (**59**) and the alcohol (**60**) may be used as sources of the iminium salt (**61**) in reactions with a wide variety of nucleophiles. In practice, it was found feasible to use Grignard reagents for reaction with the silyl derivative, while $TiCl_4$ was effective in promoting attack on the carbinol amine by weaker nucleophiles. The process is shown in Scheme 24 using the addition of indole as an example.

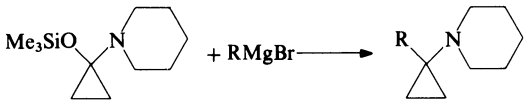


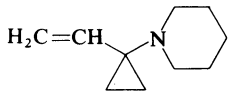
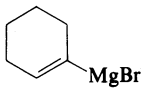
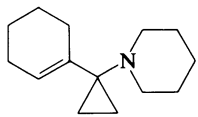
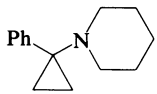
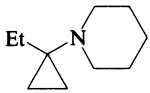
SCHEME 24

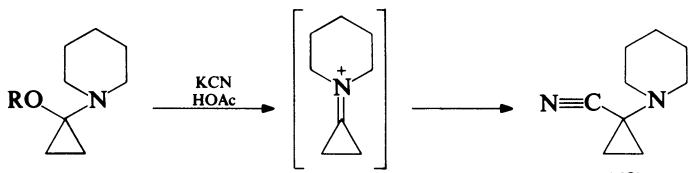
Table 11 summarizes the reactions of various Grignard reagents with **59** while Table 12 lists the $TiCl_4$-catalyzed additions to the carbinol amine **60**.

Among the nucleophiles which readily add to the presumed iminium salt intermediate is cyanide ion leading to 1-piperidino-1-cyanocyclopropane (**62**) (equation 34)[114b]. This product is of special interest because it can readily be converted to cyclopropylketimines

TABLE 11. Cyclopropane derivatives from the reaction of Grignard reagents with 1-piperidinocyclopropanol silyl ethers[114]



RMgBr	Product	Yield (%)
$H_2C{=}CHMgBr$		67
		95
PhMgBr		79
EtMgBr		92



(34)

(62)

which have found use as precursors of pyrrolines, pyrroles and other heterocyclic molecules as summarized in Schemes 25 and 26.

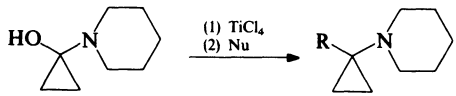
The formation of pyrroles by the reaction of the cyclopropylketimine (**63**) with HBF_4 has been studied from a mechanistic point of view using 3-chloropropionyl chloride enriched with ^{13}C at the carbonyl carbon atom[115]. The ^{13}C-NMR spectrum of the pyrrole formed from the cyclopropyl ketimine (**63**) shows enhancement of the ^{13}C peak at the 5-carbon in accord with mechanism A outlined in Scheme 27. Operation of process B analogous to the vinylcyclopropane rearrangement **63a** would have led to ^{13}C enrichment at the 3-carbon of the pyrrole product.

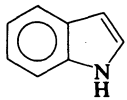
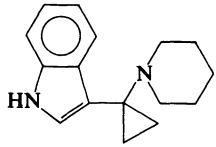
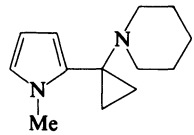
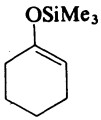
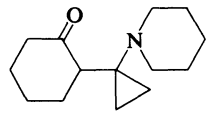
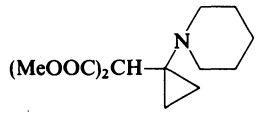
B. Preparation of Other 1,1-Disubstituted Cyclopropanones

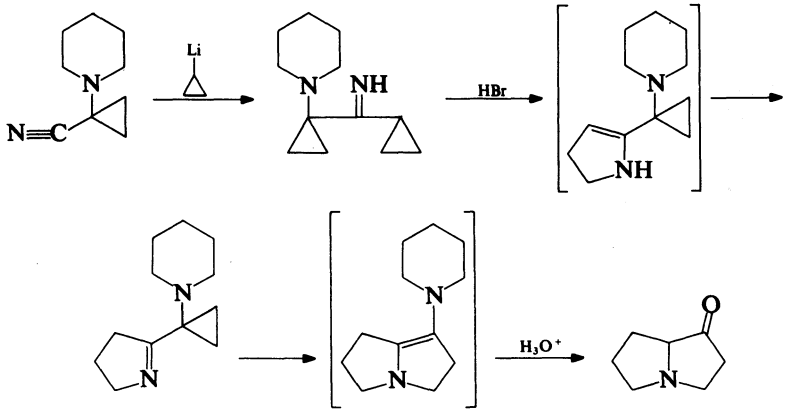
1. Carbene addition to olefins

A number of 1,1-diheteroatom-substituted cyclopropanes have been prepared by the addition of one-carbon fragments (carbenes or carbenoids) to olefins. Since the geminally

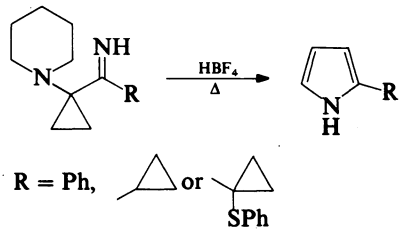
TABLE 12. Cyclopropane derivatives by the treatment of 1-piperidinocyclopropanol with titanium tetrachloride and donor reagents[114]



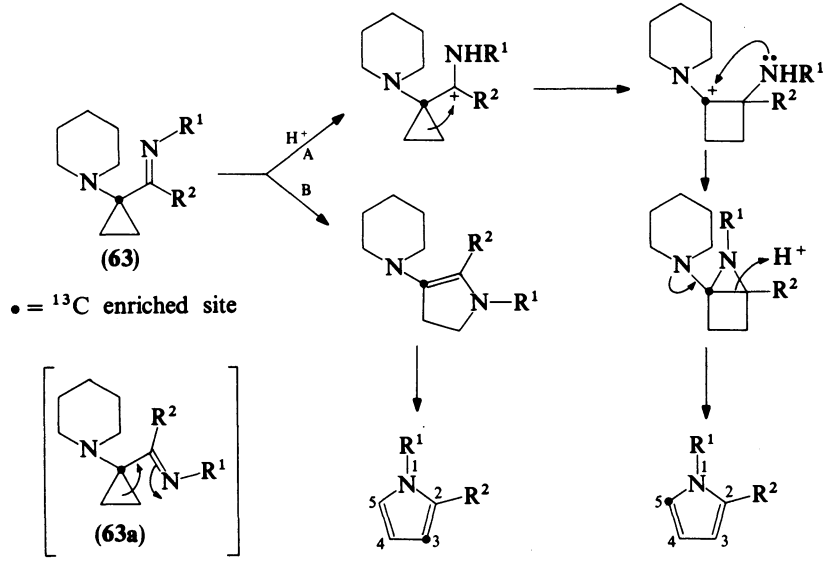
Nucleophile (Nu)	Product	Yield (%)
		84
		65
		63
$(MeOOC)_2CH_2$		55



SCHEME 25

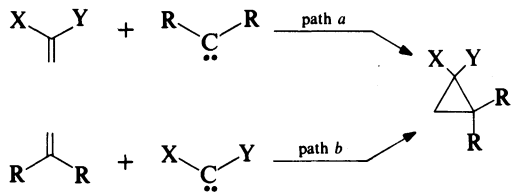


SCHEME 26

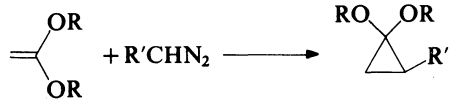


SCHEME 27

substituted heteroatoms can originate in either the carbene or olefin portion, two variants are possible (Scheme 28). One pathway (*a*) involves the addition of one-carbon fragments to ketene ketals (**64**). A number of such additions have been demonstrated and are discussed below. Treatment of **64** with diazoalkanes gives cyclopropanone ketals (**65**) as shown in equation 35 and in Table 13. Attempts to extend this reaction to the synthesis of

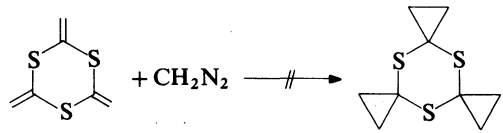


SCHEME 28



(64) (65) (35)

cyclopropanone dithioketals, i.e. **66**, have proven unsuccessful (equation 36). Ketene ketals react under various Simmons–Smith cyclopropanation conditions to give cyclopropanone ketals[19, 116, 117]. These results are listed in Table 14. A variety of other carbenes have been found to add to ketene ketals as shown in Table 15.



(66) (36)

In the path b process, the addition of a heterosubstituted carbene to an olefin is governed by the reactivity of each component. Bis-thiomethyl- and bis-thiobenzylcarbenes add only to electron-rich olefins, whereas dimethoxycarbene adds primarily to electron-poor systems. Ambiphilic carbenes such as phenoxychlorocarbene and methoxychlorocarbene add to a wide range of double bonds. Table 16 lists the cyclopropanone equivalents which have been prepared in this manner.

The yields of cyclopropanone equivalents from carbene additions to double bonds are generally poor. These preparations suffer from a variety of side reactions. Carbene dimerization is a problem in nearly all cases. In addition, the strongly alkaline conditions used in generating many of the carbenes lead to decomposition of the initially formed cyclopropanone ketals. Rearrangement of the cyclopropanones can occur even under non-basic conditions. The addition of thermally generated methoxychlorocarbene to acrolein gives butenolide (**70**) as the main product[118]. This may arise by the reaction sequence, **67** → **68** → **69** → **70** as shown in Scheme 29. Alternatively, **70** could arise from initial attack of the carbene at the carbonyl oxygen followed by ring-closure and hydrolysis **71** → **69** → **70**.

2. *Cyclization procedures*

Cyclopropanone ketals have been synthesized by several cyclization processes. Eliminative cyclization of appropriately functionalized propanes (**72**) is a particularly effective and general method (equation 37). Many anion stabilizing groups X and Y have been successfully employed in combination with a number of different leaving groups, Z.

Treatment of trithiane (**73**) with potassium amide (Table 17) gives spiro compound **74** in good yield[119]. Other dithioketal examples are shown. Cyclopropanone diselenoketals, i.e. **75**, have been prepared analogously (Scheme 30)[120].

Cohen and Daniewski have shown that thiophenol can act as a leaving group when 1,1,3-tris(thiophenyl) alkanes are treated with methyl lithium in THF (Scheme 31, Table 18)[121]. The reaction appears to go by a direct S_N2 attack of the anion (**76a**) even though surprisingly high yields are obtained in cases requiring reaction with a bulky nucleophile at the site of a sterically hindered carbon atom (see Table 18). Labeling experiments and stereochemical studies have conclusively ruled out alternative electron transfer and carbene mechanisms[121, 122]. Scheme 32 shows that the anionic intermediate **76** can also be

TABLE 13. Cyclopropanone ketals by the diazoalkane–ketene ketal reaction[41]

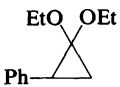
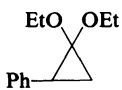
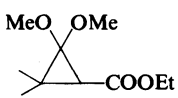
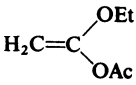
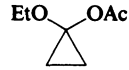
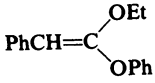
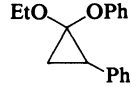
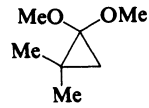
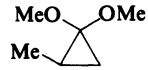
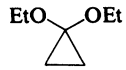
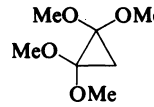
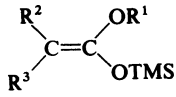
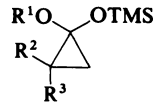
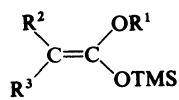
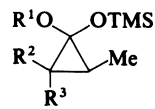
Ketene	Diazoalkane	Products	Yield (%)	Conditions	Ref.
$H_2C{=}C(OEt)_2$	CH_2N_2		40	CuBr catalyst	196
$PhCH{=}C(OEt)_2$	CH_2N_2		12	CuBr catalyst	196
$H_2C{=}C(OEt)_2$	$PhCHN_2$		82	CuBr catalyst	196
$(Me)_2C{=}C(OMe)_2$	$N_2CHCOOEt$			Cu-Bronze	196

TABLE 14. Cyclopropanone ketals by the Simmons–Smith cyclopropanation of ketene ketals

Ketene ketal	Conditions	Cyclopropanone ketal	Yield (%)	Ref.
	CH_2I_2, Zn/Cu glyme		35	199
	CH_2I_2, Zn/Cu glyme		19	199
$Me_2C{=}C(OMe)_2$	CH_2I_2, Zn/Cu CH_2I_2, Zn/Ag CH_2I_2, Zn/Cu		— 18 70	186 159 116
$MeCH{=}C(OMe)_2$	CH_2I_2, Zn/Ag		59	159
$H_2C{=}C(OEt)_2$	CH_2I_2, Zn/Ag		60	159
$(MeO)_2C{=}C(OMe)_2$	$(ICH_2)_2Zn$		20	189
	CH_2I_2, Et_2Zn			

R^1	R^2	R^3		
Bz	Me	H	90	117
Me	C_5H_{11}	H	76	
Me	Ph	H	85	
Me	Me	Me	70	
Me	$-(CH_2)_5-$		80	
TMS	C_5H_{11}	H	80	
TMS	$-(CH_2)_5-$		80	

	$MeCHI_2$, Et_2Zn			

R^1	R^2	R^3		
Me	Ph	H	86	117
Me	$-(CH_2)_5-$		91	

TABLE 14. *Continued*

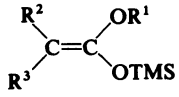
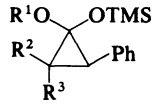
Ketene ketal	Conditions	Cyclopropanone ketal	Yield (%)	Ref.
	$PhCHI_2$, Et_2Zn			
R′ R^2 R^3				
Me Ph H			68	117
Me $-(CH_2)_5-$			64	

TABLE 15. Cyclopropanone ketals from carbene additions

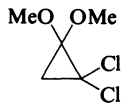
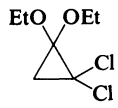
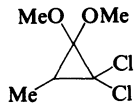
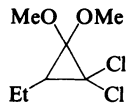
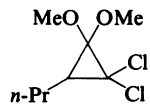
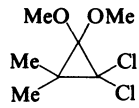
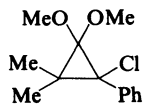
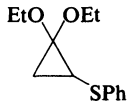
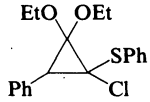
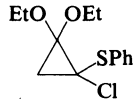
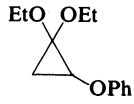
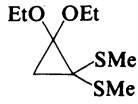
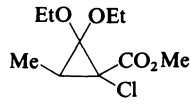
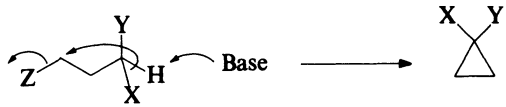
Ketene	Carbene source	Cyclopropanone ketal	Yield (%)	Ref.
$CH_2=C(OMe)_2$	$CHCl_3$, *t*-BuONa		40	100
	$CHCl_3$, NaOH		62	190
$CH_2=C(OEt)_2$	$CHCl_3$, *t*-BuONa		68	100
$MeCH=C(OMe)_2$	$CHCl_3$, *t*-BuONa		52	100
$EtCH=C(OMe)_2$	$CHCl_3$, *t*-BuONa		56	100
n-$PrCH=C(OMe)_2$	$CHCl_3$, *t*-BuONa		55	100
$Me_2C=C(OMe)_2$	$CHCl_3$, *t*-BuONa		61	100
$Me_2C=C(OMe)_2$	$PhCHCl_2$, *t*-BuONa		77	100

TABLE 15. *Continued*

Ketene	Carbene source	Cyclopropanone ketal	Yield (%)	Ref.
$CH_2=C(OEt)_2$	$ClCH_2SPh$, *n*-BuLi		80	191, 192
$PhCH=C(OEt)_2$	Cl_2CHSPh, *t*-BuOK		—	193
$CH_2=C(OEt)_2$	Cl_2CHSPh, *t*-BuOK		40–60	193
$CH_2=C(OEt)_2$	$ClCH_2OPh$, BuLi		33	194
$CH_2=C(OEt)_2$	$TsNHN=C(SMe)_2$, NaH		30	195
$MeCH=C(OEt)_2$	$PhHgC(Cl)_2CO_2Me$			196



(72) (37)

formed by addition of sulfur-stabilized anions (**77**) to dithioketene ketals (**78a**) in a connective process leading ultimately to cyclopropanone dithioketals (**79a**)[123]. Similar additions to 1-thiophenyl-1-trimethylsilylethylene (**78b**) give 1-thiophenyl-1-trimethylsilylcyclopropanes (**79b**)[124].

Cyclopropane cyanohydrin (**83**) has been synthesized by the cyclodehydrohalogenation of protected chloropropionaldehyde cyanohydrin (**80**) (Scheme 33)[125]. The protected cyanohydrin (**81**) is converted in two steps to cyclobutanone (**82**)[125].

Epoxides may be transformed to dithio-[126], diseleno-[120], or silyl-substituted thioketals[124] by three-step procedures (Scheme 34, Table 19). As shown in the case of ethylene oxide (**84**), the epoxides are cleaved by the appropriate stabilized anion (**85**), tosylated, and cyclized with base to give **86** in good yield.

TABLE 16. Cyclopropanone derivatives from the addition of a heterosubstituted carbene to an olefin

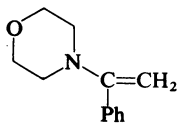
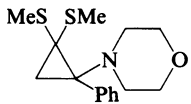
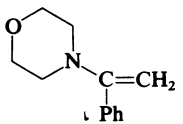
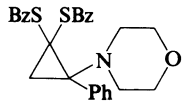
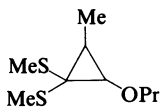
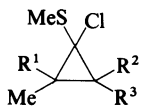
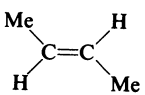
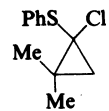
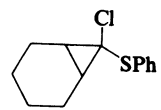
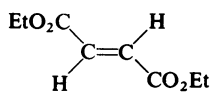
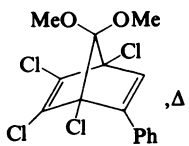
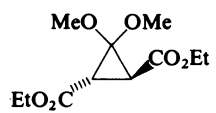
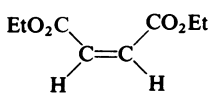
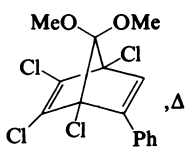
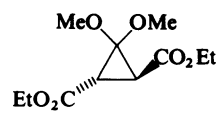
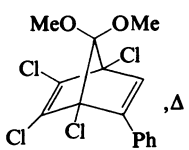
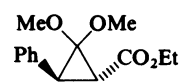
Olefin derivative	Carbene source	Cyclopropanone derivative	Yield (%)	Ref.
	$TsNHN{=}C(SMe)_2$, NaH		32	195
	$TsNHN{=}C(SMe)_2$, *t*-BuOK		23	195
	$TsNHN{=}C(SBz)_2$, NaH		8	195
MeCH=CH–OPr (*cis*)	$TsNHN{=}C(SMe)_2$, NaH		11	195
$Me_2C{=}CMe_2$	$MeSCHCl_2$, *t*-BuOK			
		$R^1 = R^2 = R^3 = Me$	28	197
$Me_2C{=}CHMe$	$MeSCHCl_2$, *t*-BuOK	$R^1 = R^3 = H$, $R^2 = Me$	15	197
$Me_2C{=}CH_2$	$MeSCHCl_2$, *t*-BuOK	$R^1 = Me$, $R^2 = R^3 = H$	17	197
	$MeSCHCl_2$, *t*-BuOK	$R^1 = R^3 = H$, $R^2 = Me$	8	197

TABLE 16. *Continued*

Olefin derivative	Carbene source	Cyclopropanone derivative	Yield (%)	Ref.
$Me_2C{=}CH_2$	Cl_3SPh, MeLi	$R^1 = Me$, $R^2 = R^3 = H$	25	145, 193
$Me_2C{=}CH_2$	Cl_2CHSPh, *t*-BuOK		50–60	193
	Cl_2CHSPh, *t*-BuOK		15–20	193
			—	146
			—	146
$PhCH{=}CHCO_2Et$			—	146

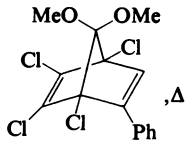
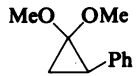
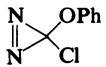
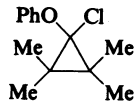
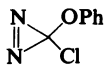
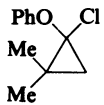
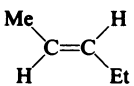
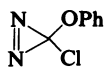
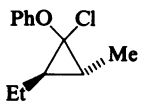
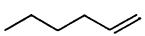
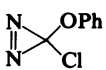
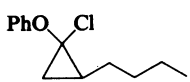
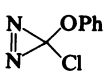
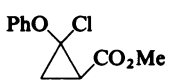
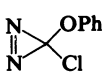
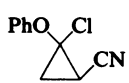
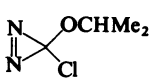
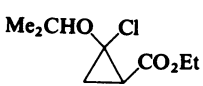
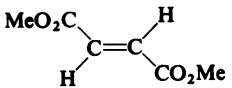
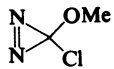
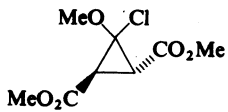
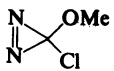
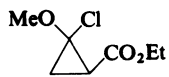
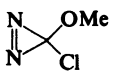
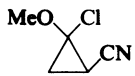
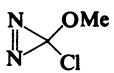
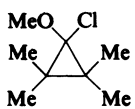
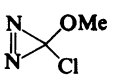
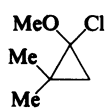
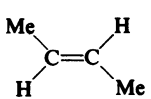
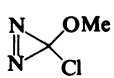
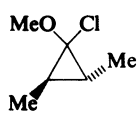
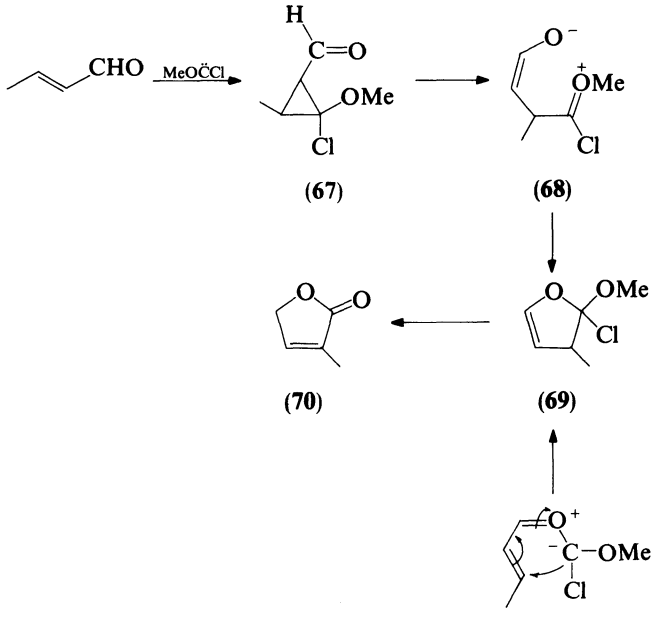
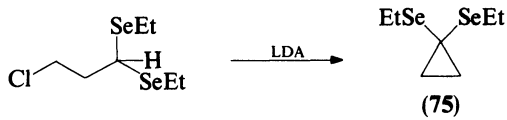
$PhCH{=}CH_2$			—	147
$Me_2C{=}CMe_2$			32	146
$Me_2C{=}CH_2$			40	148
			20	148
			10	148
$CH_2{=}CHCO_2Me$			28	148
$CH_2{=}CHCN$			30	148
$CH_2{=}CHCO_2Et$			—	118, 147

TABLE 16. *Continued*

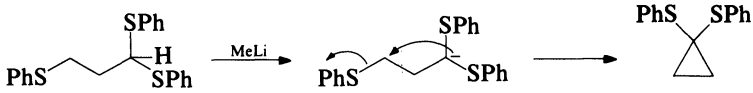
Olefin derivative	Carbene source	Cyclopropanone derivative	Yield (%)	Ref.
			21	148
CH_2=$CHCO_2Et$			—	118, 147
CH_2=CHCN			—	118, 147
Me_2C=CMe_2			—	119
Me_2C=CH_2			—	119
			—	119



SCHEME 29



SCHEME 30

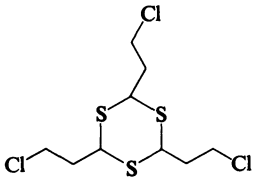
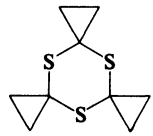
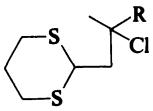
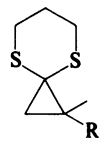
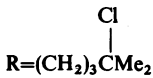
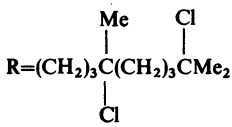
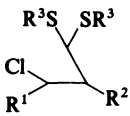
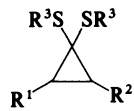


SCHEME 31

When certain β-keto-dithioesters (**87**) are treated with Grignard reagents, thiophilic addition occurs and 2-hydroxycyclopropanone dithioketals (**88**) are produced (Scheme 35)[127, 128]. Only one isomer is obtained and a concerted *cis*-homo-1,4-addition has been proposed to account for the stereospecificity observed. Along somewhat similar lines, Giusti and coworkers have synthesized several cyclopropanone ketals by treating 1,3-dibromo-2-propanone ketals with active metals (Table 20)[12]. Allenes are a byproduct in this reaction. Dihaloketals may also be cyclized electrolytically (Table 21)[129].

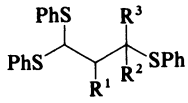
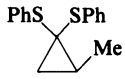
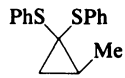
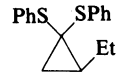
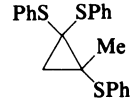
On the other hand, more easily deprotected cyclopropanone aminals and acylals could not be obtained in useful amounts by the reduction of the corresponding 1,3-dihaloacylals

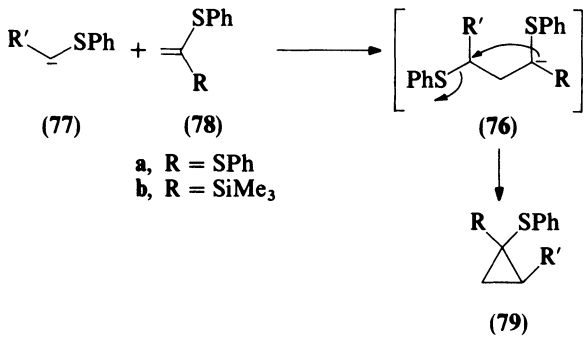
TABLE 17. Cyclopropanone dithioketals from base-catalyzed cyclization of 3-haloalkyl dithioketals[41]

Halo compound	Base	Cyclopropanone dithioketal	Yield (%)	Ref.
 (73)	KNH_2	 (74)	75	119
				
R=Me	BuLi		90	109
$R=(CH_2)_3CHMe_2$	BuLi		80	109
	BuLi		85	109
	BuLi		65	109
 R^1, R^2 = H, R^3 = Me	BuLi		73	149
$R^1 = R^2 = H$, $R^3 = Et$	BuLi		71	
$R^1 = R^2 = H$, $R^3 = i$-Pr	BuLi		60	
$R^1 = R^2 = H$, $R^3 = Bu$	BuLi		72	
$R^1 = H$, $R^2 = Me$, $R^3 = Et$	BuLi		63–68	149
$R^1 = H$, $R^2 = Et$, $R^3 = Me$	BuLi		71	
$R^1 = R^2 = R^3 = Me$	BuLi		70	
$R^1 = R^3 = Me$, $R^2 = Et$	BuLi		57–59	

and aminals[129]. As shown in Scheme 36, attempted reduction of **89** gave only products resulting from an elimination reaction. Reduction of aminal **90** in the presence of a proton source gave oxazine **92**. When no protons are available, anion **91** undergoes elimination and cyclization giving oxazepine (**93**). In this case, cyclopropane (**94**) is obtained in about 10% yield.

TABLE 18. Cyclopropanone dithioketals from 1,1,3-tris(thiophenyl) alkanes and methyl lithium[121]

	Cyclopropanone ketal	Yield (%)
$R^1 = R^2 = R^3 = H$		99
$R^1 = R^2 = H$, $R^3 = Me$		100
$R^1 = Me$, $R^2 = R^3 = H$		100
$R^1 = R^2 = H$, $R^3 = Et$		80
$R^1 = H$, $R^2 = Me$, $R^3 = SPh$		90



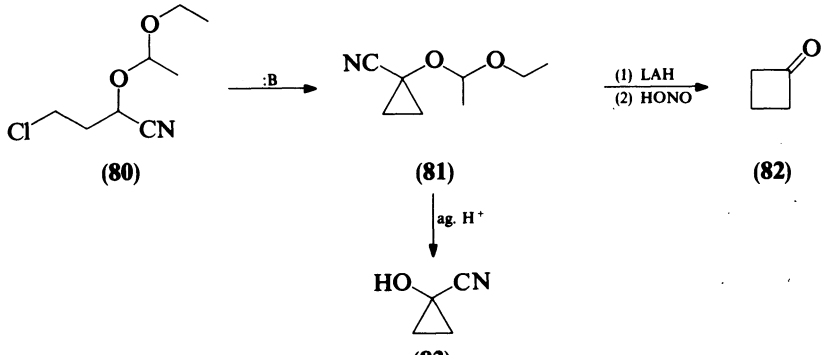
(77) (78) (76) (79)

a, R = SPh
b, R = $SiMe_3$

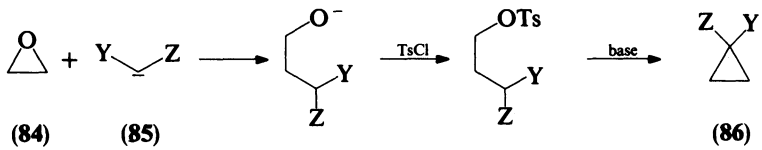
SCHEME 32

3. *1,3-Displacement reactions*

Displacement reactions on 1,1-disubstituted cyclopropanes have been used to prepare other cyclopropanone equivalents. The most readily available 1,1-disubstituted cyclopropanes are geminal dihalo derivatives prepared by the addition of dihalocarbenes to olefins. Unfortunately, these materials do not undergo direct displacement easily and therefore do not provide a general route to other cyclopropanone derivatives. Solvolysis usually leads to ring-opened products, although dibromocyclopropanes with a barrier to



SCHEME 33



SCHEME 34

TABLE 19. Cyclopropanone dithioketals from epoxides

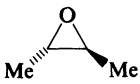
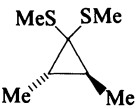
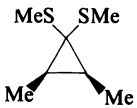
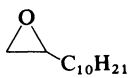
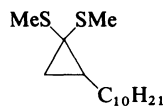
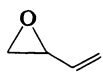
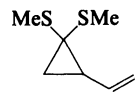
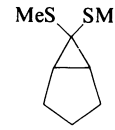
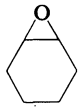
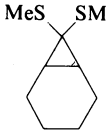
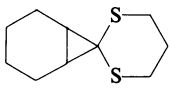
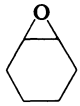
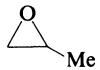
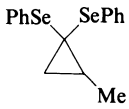
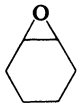
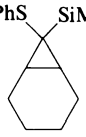
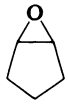
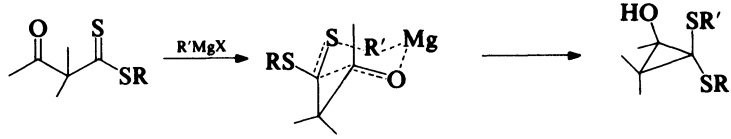
Epoxide	Anion	Cyclopropanone dithioketal	Yield (%)	Ref.
	$H\bar{C}(SMe)_2$		66	126
	$H\bar{C}(SMe)_2$		67	126
	$H\bar{C}(SMe)_2$		77	126
	$H\bar{C}(SMe)_2$		60	126

TABLE 19. *Continued*

Epoxide	Anion	Cyclopropanone dithioketal	Yield (%)	Ref.
	$H\bar{C}(SMe)_2$		70	126
	$H\bar{C}(SMe)_2$		81	126
			75	126
	$H\bar{C}(SPh)_2$		51	126
	$\bar{C}(SePh)_3$		60	124
	$Me_3Si\bar{C}HSPh$		69	124
	$Me_3Si\bar{C}HSPh$		59	124

ring-opening, i.e. **95**, have been shown to undergo silver-ion assisted solvolysis to give both cyclopropane **96** and ring-opened product **97** (Scheme 37)[130].

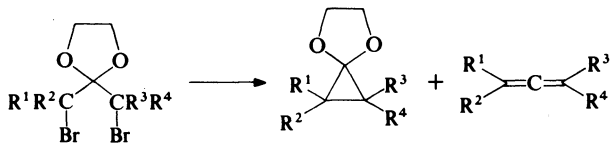
S_N2 reactions at cyclopropane rings are very difficult. Treatment of dihalocyclopropanes with strongly basic nucleophiles generally gives rearranged products[131, 132]. In a few cases (Scheme 38)[133] displacement appears to take place but this reaction most probably



(87) (88)

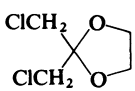
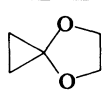
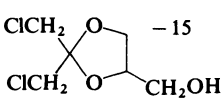
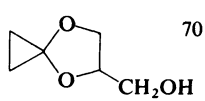
SCHEME 35

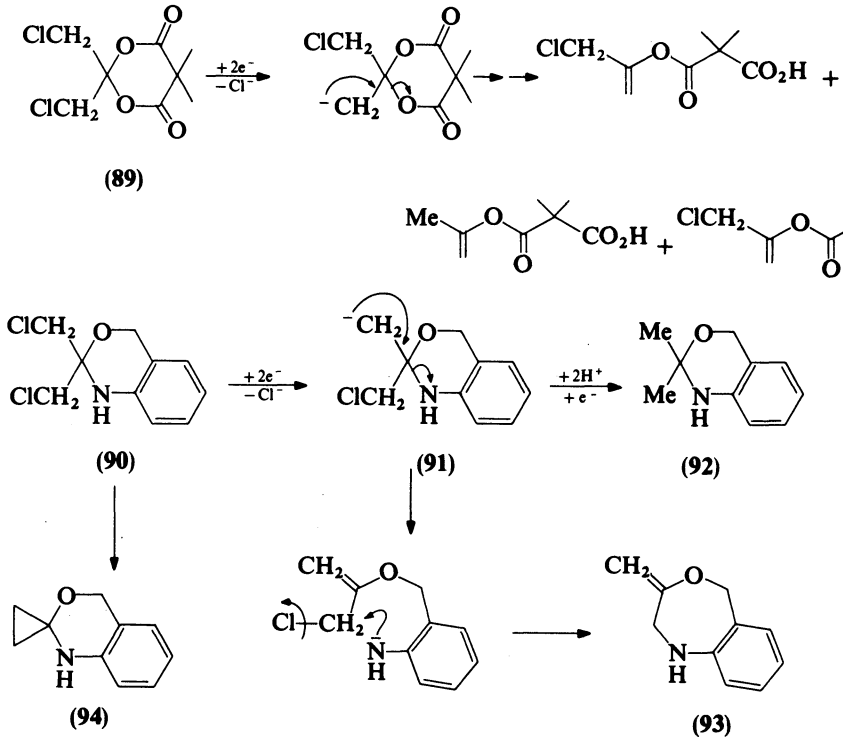
TABLE 20. Ketals from protected 1,3-dibromo-2-propanone[12,41]



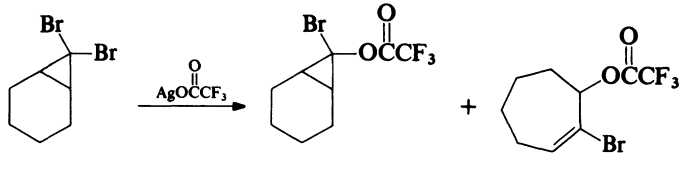
	Products (% yields)			
	Mg/THF		Zn/HMPT	
Dibromide	Allene	Ketal	Allene	Ketal
$R^1 = R^2 = R^3 = R^4 = H$	44	50	20	20
$R^1 = R^2 = R^3 = H$, $R^4 = Me$	47	37	20	23
$R^1 = R^2 = R^3 = H$, $R^4 = Et$	39	53	40	23
$R^1 = R^2 = H$, $R^3 = R^4 = Me$	37	40	50	28
$R^1 = R^3 = H$, $R^2 = Me$, $R^4 = Pr$	20	58	60	28
$R^1 = R^2 = R^3 = H$, $R^4 = C_6H_{13}$	30	60	60	20
$R^1 = R^2 = R^3 = H$, $R^4 = Ph$	19	70	—	—
$R^1 = R^3 = H$, $R^2 = R^4 = Me$	—	70	—	—
$R^1 = R^3 = H$, $R^2 = R^4 = Et$	10	75	70	20
$R^1 = R^3 = H$, R^2–$R^4 = (CH_2)_3$	—	93	—	—
$R^1 = R^3 = H$, R^2–$R^4 = (CH_2)_4$	—	83	—	—

TABLE 21. Cyclopropanone ketals from electrolytical reduction of dihaloketals[129]

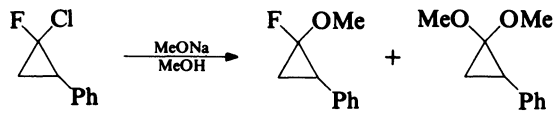
Dihaloketal (0.1 mol l^{-1})	Temperature (°C)	Potential (V vs. SCE)	Current density ($mAcm^{-2}$)	Cyclopropanone ketal	Yield (%)
	0	−2.56	25		75
	−15	−2.76	25		70



SCHEME 36



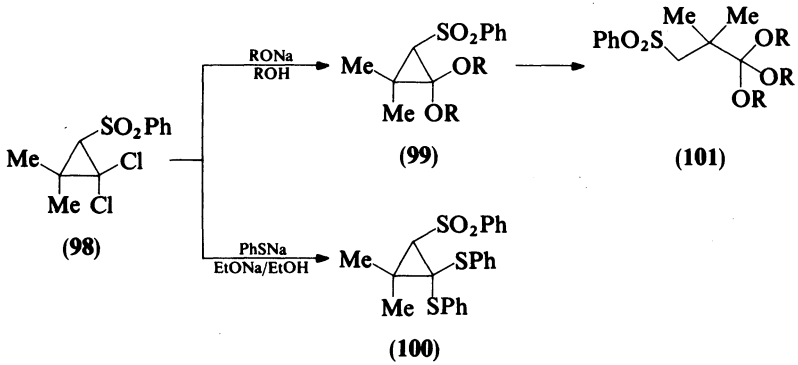
SCHEME 37



SCHEME 38

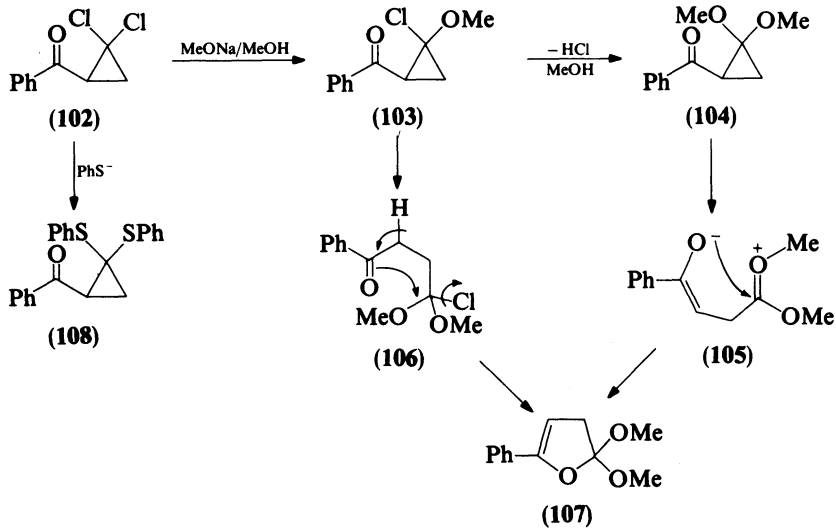
involves a two-step elimination–addition process. Carbonyl or sulfonyl groups in the 2-position greatly facilitate each of these two steps. Thus, Parham and coworkers found that treatment of 2-phenylsulfonyl-1,1-dichloro-3,3-dimethylcyclopropane (**98**) with alkoxides or thiolates gave cyclopropanone ketals (**99**) and dithioketals (**100**), respectively

(Scheme 39)[134]. The 2-phenylsulfonyl cyclopropanone ketals could be converted to orthoesters (**101**) on prolonged treatment with alkoxides.

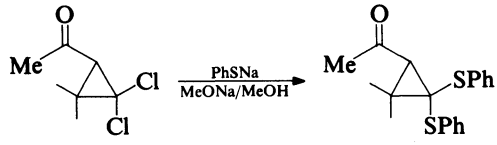


SCHEME 39

Tishchenko and coworkers obtained dihydrofuran derivatives when 2-benzoyl-1,1-dichlorocyclopropane (**102**) was treated with alkoxides (Scheme 40)[135]. Product (**107**) is highly reminiscent of butenolide (**70**) obtained by the addition of chloromethoxycarbene to acrolein as discussed earlier (Scheme 29) and may result from ring-opening of cyclopropanone ketal (**104**). Perhaps a more likely mechanism involves addition of alkoxide to intermediate **103** followed by cyclization **106** → **107**. When treated with thiophenoxide, **102** gave cyclopropanone dithioketal (**108**). A similar result has been obtained by Banwell (Scheme 41)[136]. Treatment of **109** with thiophenoxide gave dithioketal **110** in 98% yield. In contrast to the results of Tishchenko, however, keto ester products (**112**) were obtained from 2,2-dichloro-1-acylcyclopropanes (**111**) and alkoxides (Scheme 42)[136].

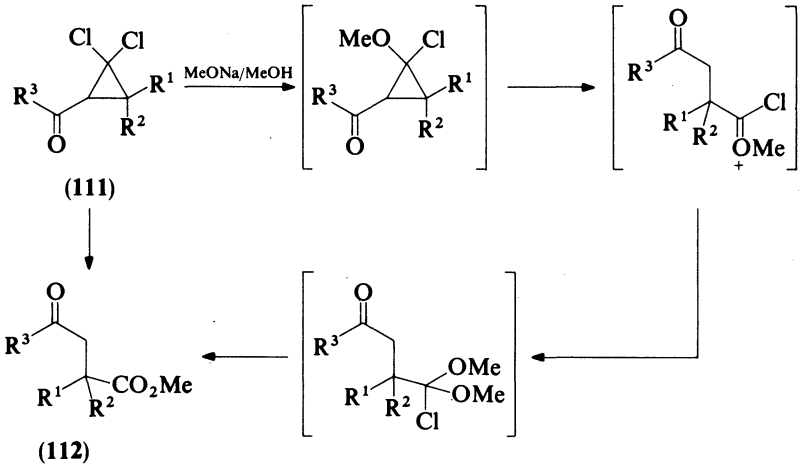


SCHEME 40



(109) (110)

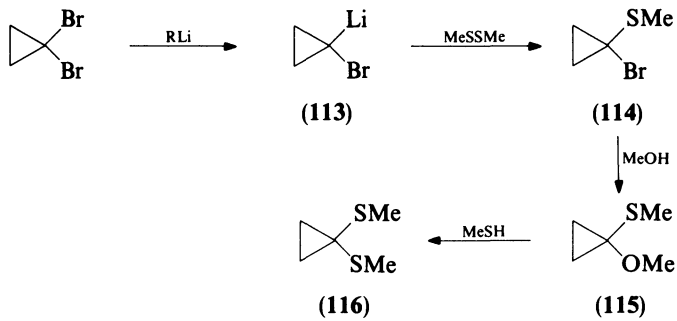
SCHEME 41



(111) (112)

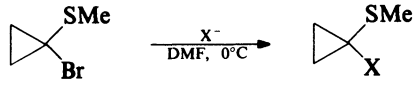
SCHEME 42

Gem-dibromocyclopropanes can be converted into synthetically useful cyclopropanone equivalents by a process consisting of lithium–halogen exchange followed by reaction of lithiocyclopropane (**113**) with dimethyl disulfide (Scheme 43)[126]. The resulting bromomethylthio derivative (**114**) undergoes a variety of substitution reactions. Methanolysis gives *S,O*-dimethylketal (**115**)[126, 137] which can be converted into 1,1-bis(methylthio)cyclopropane (**116**) with methyl mercaptan in trifluoroacetic acid[126]. Reaction of **114** with other nucleophiles provides the derivatives shown in Scheme 44[138]. The sulfur-



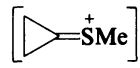
(113) (114) (115) (116)

SCHEME 43



(114) (118)

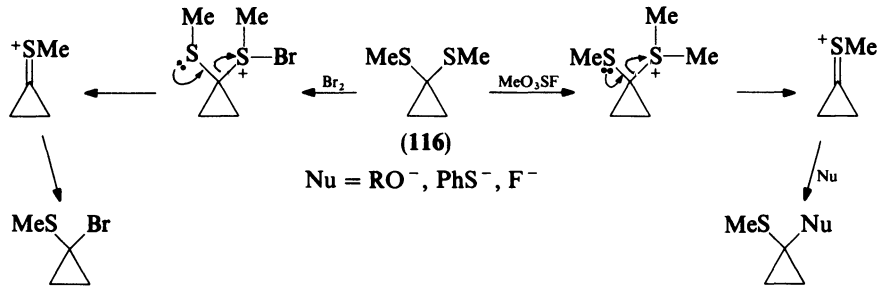
$X^- = HCOO^-, I^-, N_3^-, HS^-$



(117)

SCHEME 44

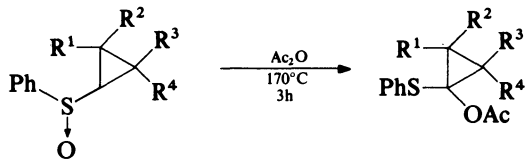
stabilized cation (**117**) is presumed to be the intermediate in all of the reactions. The same intermediate can be generated by treating **116** with bromine or with methyl fluorosulfonate (Scheme 45)[138].



SCHEME 45

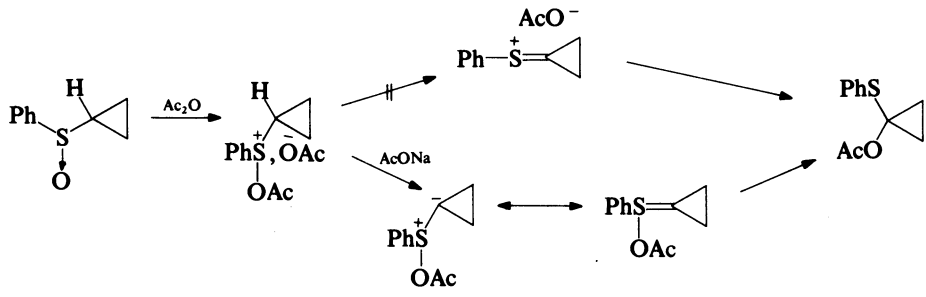
4. Miscellaneous

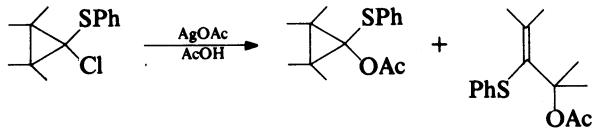
In their study of the Pummerer reaction, Oae and coworkers found that treatment of phenylsulfinylcyclopropanes (**119**) with acetic anhydride led to 1-phenylthio-1-acetoxycyclopropanes (**120**) in good yields (Scheme 46)[139]. This stereoselective rearrangement was unaccompanied by ring-opened products suggesting that the reaction proceeded via a non-carbenium ion pathway (Scheme 47)[139–141]. The authors observed varying amounts of ring-opened products (**121**) in the solvolysis of 1-chloro-1-(phenylthio)cyclopropanes (**122**), reactions presumed to involve carbenium ions. As had been noted earlier, alkyl groups on the cyclopropane ring tend to increase the yield of ring-



(119) (120)

SCHEME 46





(122) **(121)**

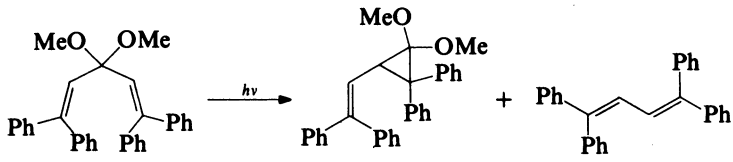
SCHEME 47

opened product[138]. It should be noted, however, that no ring-opened material has been observed in the solvolysis of **123**[137] or **124**[126].

(123) **(124)**

Pummerer-type chlorination of phenylsulfinylcyclopropanes provides a high-yield route to 1-phenylthio-1-chlorocyclopropanes[142, 143]. Table 22 lists the results from a variety of chlorinating agents.

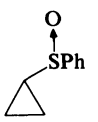
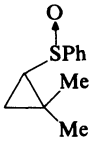
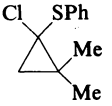
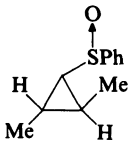
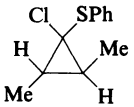
The tetraphenyldiene **125** (Scheme 48) undergoes a photochemical rearrangement yielding cyclopropanone ketal (**126**) and tetraphenylbutadiene[144].



(125) **(126)**

SCHEME 48

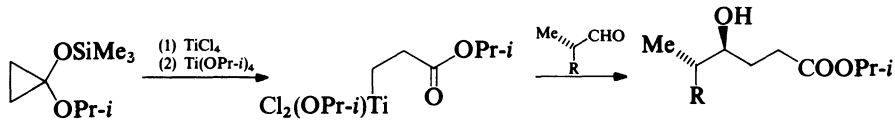
TABLE 22. 1-Phenylthio-1-chlorocyclopropanes from Pummerer-type chlorination of phenylsulfinylcyclopropanes[142]

Phenylsulfinyl cyclopropane	Chlorinating agent	Product	Yield (%)
	$SOCl_2$ EtCOCl $PhICl_2$ SO_2Cl_2		100 100 92 85
	$SOCl_2$ $PhICl_2$		71 86
	$SOCl_2$ $PhICl_2$		85 87

VII. REACTIONS OF SUBSTITUTED CYCLOPROPANONE EQUIVALENTS

A. Ring-opening Reactions

Ring-opening reactions of cyclopropanone hemiketals are well known. Under appropriate conditions, cleavage of trimethylsilyl protected hemiketals can provide a synthetically useful route to homoenolate anions as noted earlier (Scheme 20). The reaction of an isopropoxy-titanium homoenolate (**128**) derived from **127** with an aldehyde has recently been used as the key step in the stereocontrolled construction of the steroidal side-chain of depresosterol (Scheme 49)[102b].

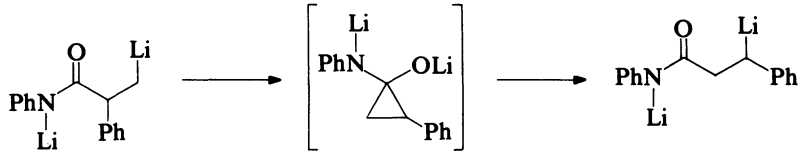


(**127**) (**128**)

SCHEME 49

The homoenolate dianion **129** rearranges to the more stable species **130** presumably through dilithiocyclopropane intermediate **131** (Scheme 50)[150]. Other electrophilic species can take the place of a proton in this ring-cleavage reaction. Table 23 lists representative examples.

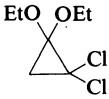
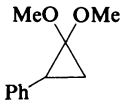
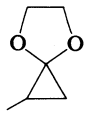
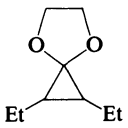
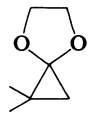
Ring-opening reactions of cyclopropane dithioketals are synthetically useful. Seebach and coworkers have developed a method for inserting a carbonyl group between the sp^2 carbons of an olefin[126, 151]. As discussed earlier (Scheme 43), addition of dibromocarbene



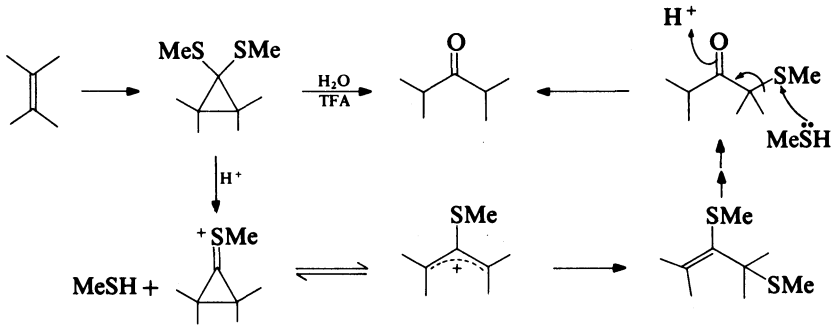
(129) (131) (130)

SCHEME 50

TABLE 23. Electrophilic reactions of cyclopropanone ketals[41]

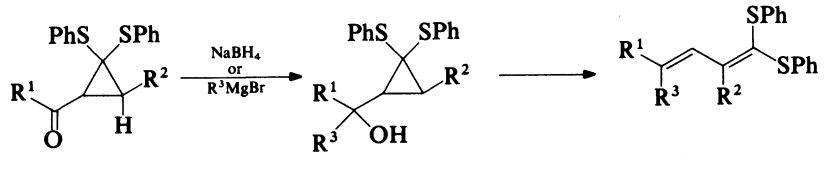
Ketal	Electrophile	Products, yields % and reaction conditions	Ref.
	Br_2/CCl_4	$BrCH_2CH_2COOEt + BrCH_2CH(Br)COOEt$ (41) (39)	100
	Br_2/CCl_4	$Cl_2C(Br)CH_2COOEt$ (77)	100
	Br_2/CCl_4	$BrCH_2C(Me)_2COOMe$ (~ 100)	186
	Br_2/SO_2	$BrCH_2CH_2COOMe$	180
	Br_2/SO_2	$PhCH(Br)CH_2COOMe$	180
	$ClOH/H_2O$	$ClCH_2CH(Me)COOCH_2CH_2OH$, 5°C (88)	101
	n-BuSH	*i*-$PrCOOCH_2CH_2SBu$-*n*, 180°C, 24 h (90)	101
	PhOH	*n*-$PrCH(Et)COOCH_2CH_2OPh$, 100°C, 24 h (50)	101
	H_2O, H^+	*n*-$PrCH(Et)COOCH_2CH_2OH$, 100°C, 2 h (80)	
	Br_2/CCl_4	$BrCH_2C(Me)_2COOCH_2CH_2Br$, 0°C (85)	101

to an olefin followed by lithium–halogen exchange and reaction with dimethyl disulfide gives a bromo(methylthio)cyclopropane which can be converted in two steps to the dithioketal. Aqueous trifluoroacetic acid converts the dithioketal to a carbonyl compound and dimethyl disulfide by the mechanism shown in Scheme 51 (Table 24).



SCHEME 51

Secondary benzylic or tertiary alcohols (**132**) resulting from the reduction of, or Grignard addition to 2-acyl-1,1-bis(phenylthio)cyclopropanes (**133**) undergo dehydration and ring-opening to give α,β-unsaturated ketene dithioketals (**134**) in high yield (Scheme 52)[152].



(**133**) (**132**) (**134**)

SCHEME 52

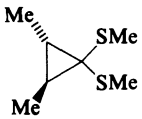
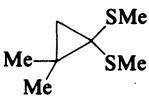
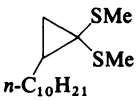
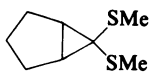
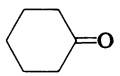
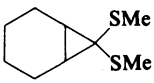
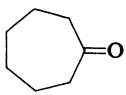
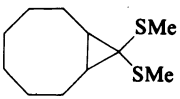
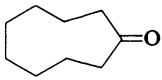
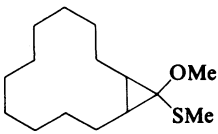
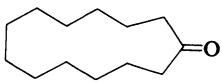
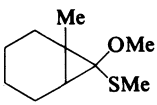
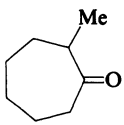
For geminally substituted cyclopropanes, the bond which is cleaved by catalytic hydrogenation is determined by the electronic nature of the substituents. Electron-donating groups promote C(2)–C(3) bond cleavage whereas electron-withdrawing substituents tend to promote C(1)–C(2) bond cleavage (Scheme 53)[153]. These generalizations are borne out by many examples including the observation that coprin (**135**) is hydrogenated to isopropyl amine and acetone[154].

B. Other Substitution Processes

As discussed in an earlier section, displacement reactions on appropriately 1,1-disubstituted cyclopropanes may give rise to new cyclopropanone equivalents (see Schemes 43, 44). These reactions occur by S_N1 processes[137] involving carbenium ions of structure **136**. In addition to being susceptible to ring-opening (Scheme 18) and trapping

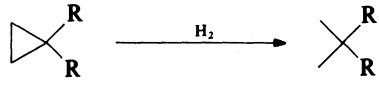
(**136**)

TABLE 24. Ketones from ring-opening of cyclopropane monothio or dithioketals.

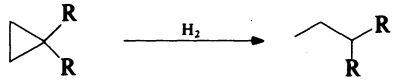
Cyclopropanone monothio or dithioketal	ketone	Yield (%)
	EtCOEt	55
	MeCOPr-i	75
	$MeCOC_{11}H_{23}$-n	85
		55
		90
		83
		65
		78

by the nucleophiles mentioned previously, these stabilized ions can participate in a Friedel–Crafts type of reaction (Scheme 54)[138]. Solvolysis of 1-bromo-1-methylthiocyclopropane (**137**) in trifluoroethanol in the presence of furan leads to adducts **138** and **139**. Compound **140** undergoes an intramolecular alkylation to give sulfide **141**, whereas **142** undergoes solvolysis, ring-opening to intermediate **143** and intramolecular alkylation to give indene (**144**).

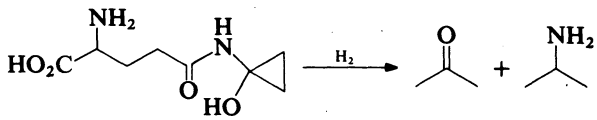
Cyclopropanone dithio- (**145**)[155, 156], diseleno- (**146**)[120] and silyl-thioketals (**147**)[124, 156] undergo lithiation, generating synthetically useful salts **148**, **149** and **150**, respectively (Scheme 55). Each anion may undergo reaction with carbonyl compounds.



R = Me, OH, OCH_3, OCOMe

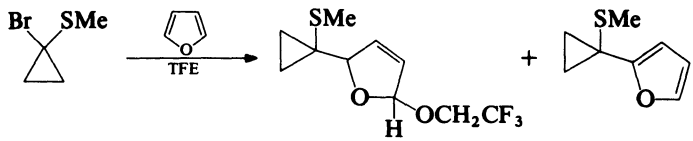


R = CO_2H, CN, $CONH_2$

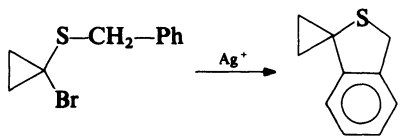


(135)

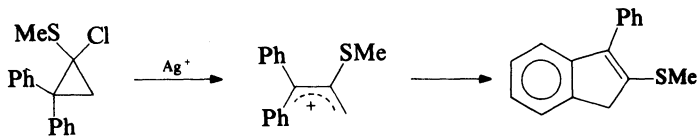
SCHEME 53



(137) (138) (139)



(140) (141)



(142) (143) (144)

SCHEME 54

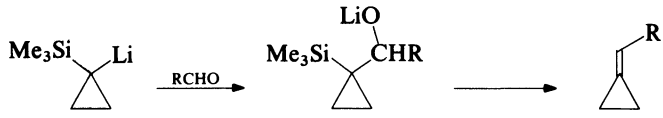
Thus, the alkoxides generated from silyl derivatives (**150**) undergo the Petersen reaction yielding olefins (Scheme 56)[124, 156].

C. Cycloaddition Reactions

Cyclopropanone ketals undergo a unique $[2_s + 2_a]$ cycloaddition reaction with tetracyanoethylene (TCNE)[157–159]. In the case of *cis*- and *trans*-dimethyl *O,S* ketals **151**

(145) X = SPh, Y = SPh (148)
(146) X = SePh, Y = SePh (149)
(147) X = SPh, Y = $SiMe_3$ (150)

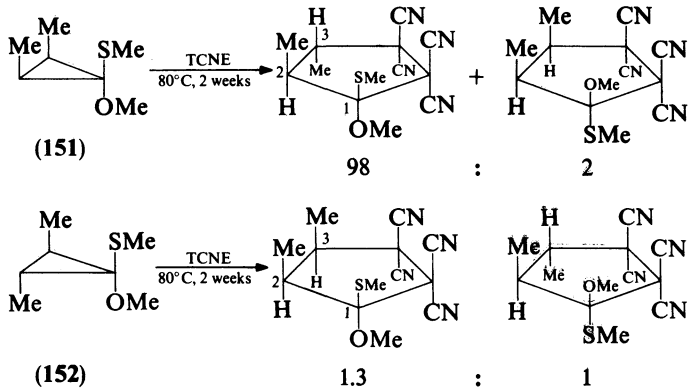
SCHEME 55



(150)

SCHEME 56

and **152**, the reactions occur in a stereoselective manner (Scheme 57)[158]. Product ratios are not affected by solvent polarities and dimeric species have not been observed. A mechanism involving polar and radical intermediates seems less likely than one featuring a concerted cycloaddition.



(151) 98 : 2

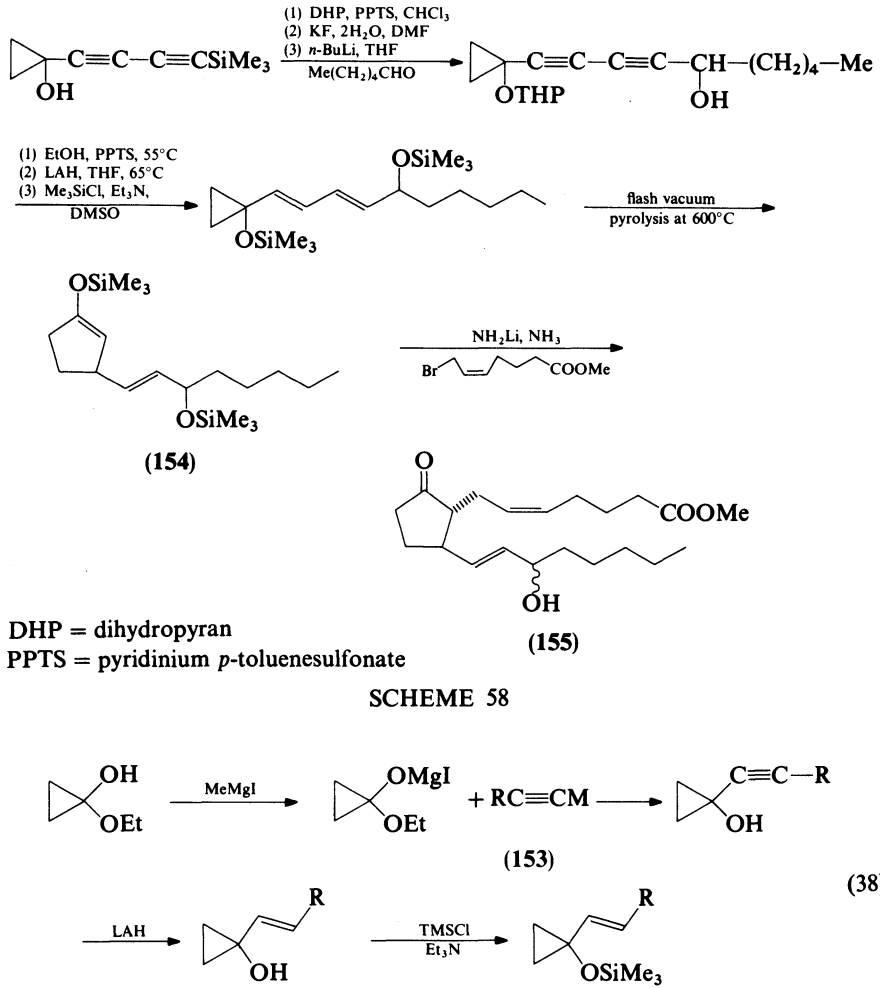
(152) 1.3 : 1

SCHEME 57

VIII. CYCLOPROPANONES IN SYNTHESIS

Cyclopropanones have been used as unique sources of three-carbon units in various synthetic applications including the synthesis of natural products. In general, the sources of the ketones have been the readily available hemiketals or their derivatives as is illustrated in Scheme 49[102b] and in the formation of (+)-11-deoxyprostaglandin E_2 methyl ester (Scheme 58)[160].

Cyclopropanone ethyl hemiketal was converted to the vinyltrimethylsiloxy cyclopropane by the addition of the acetylenic nucleophile **153**, followed by the steps shown in equation 38 and Scheme 58. Thermal ring enlargement provided the 3-substituted



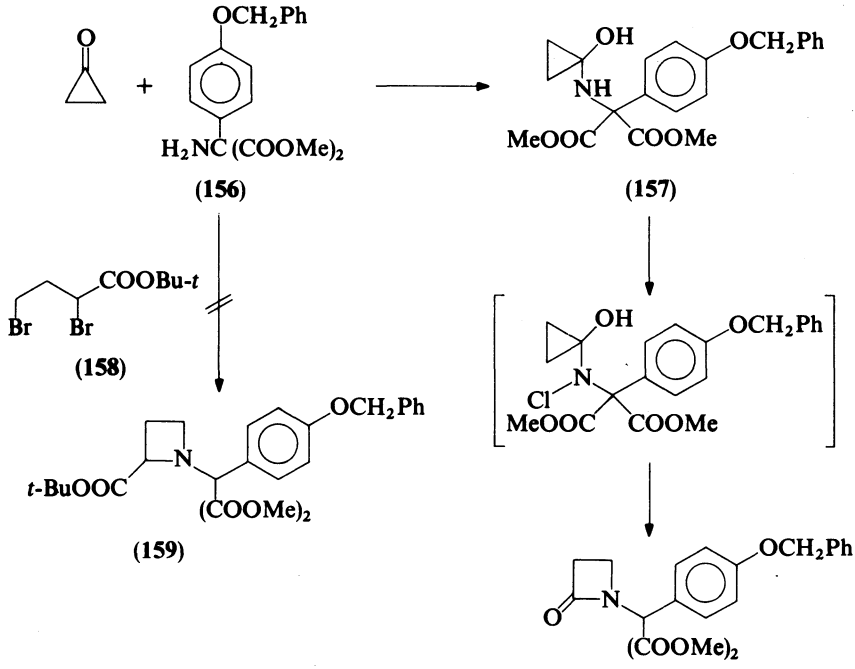
DHP = dihydropyran
PPTS = pyridinium *p*-toluenesulfonate

SCHEME 58

(38)

cyclopentanone silyl enol ether (**154**) which could then be transformed to the target product (**155**) by the sequence shown. The key reaction in this route, the thermal vinylcyclopropane to cyclopentene rearrangement, was studied in detail by Salaun during his investigations of the use of cyclopropanone hemiketals in synthesis.

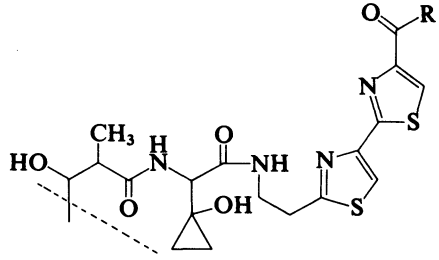
In the course of studies on cyclopropanone—β-lactam conversions, Wasserman and coworkers[161,162] developed a route to the nocardicins by taking advantage of the reactivity of primary amines with cyclopropanone. The unusual susceptibility of the carbonyl group of cyclopropanone to attack by nucleophiles is well exemplified in this synthesis which involves the addition of the highly hindered malonate derivative (**156**) to generate the cyclopropanol adduct (**157**). The hindered amine (**156**) was previously found to be completely unreactive as a nucleophile in a displacement reaction with dibromoester (**158**) in an attempt to form the azetidine carboxylate (**159**). The further conversion of the amino malonate adduct (**157**) to the β-lactam through a nitrenium ion rearrangement is illustrated in Scheme 59.



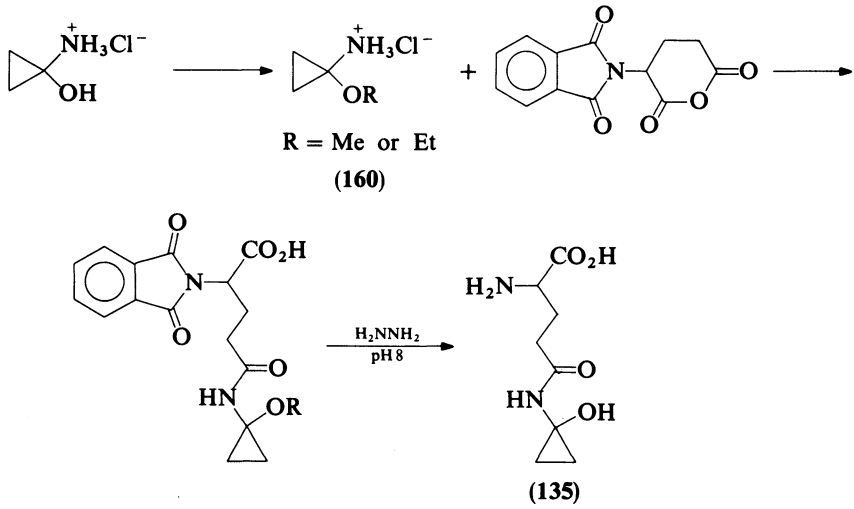
SCHEME 59

The recent isolation of coprine **135** (N^5-(1-hydroxycyclopropyl)-L-glutamine) from the inky cap mushroom *Coprinus atramentarius* has focused fresh attention on the chemistry of cyclopropanone and its derivatives. This product has been shown to be responsible for the 'Antabuse-like' action of this fungus. The synthesis of coprine which served to confirm the structure and to provide material for pharmacological studies is outlined in Scheme 60[163]. Reaction of cyclopropanone, formed according to the van Tilborg procedure[164], with ammonia, and trapping the adduct with HCl, gave a low yield of the corresponding amine hydrochloride. However, a high yield of this product could be obtained by hydrolysis of 1-ethoxycyclopropyl isocyanate formed by the Koch procedure[23]. Acylation of **160** with *N*-phthaloyl-L-glutamic acid anhydride and subsequent removal of the blocking group with hydrazine at pH 8 yielded coprine (**135**).

For the synthesis of cleonine, a novel amino acid incorporated in the antibiotic cleomycin (**161**), Kato and coworkers[165] used the readily available cyclopropanone

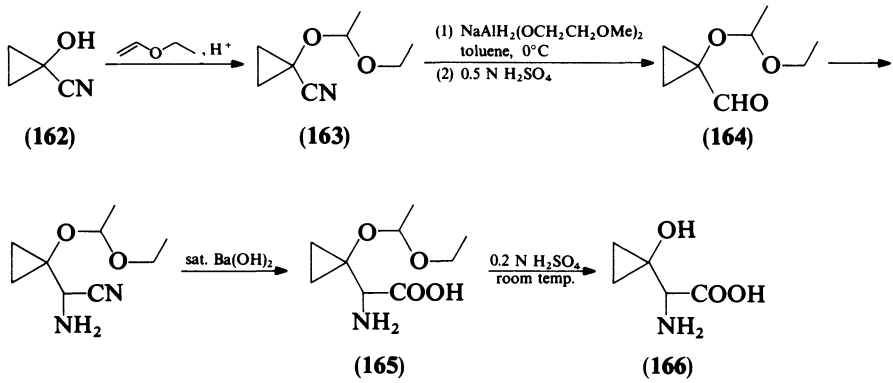


(161) partial structure



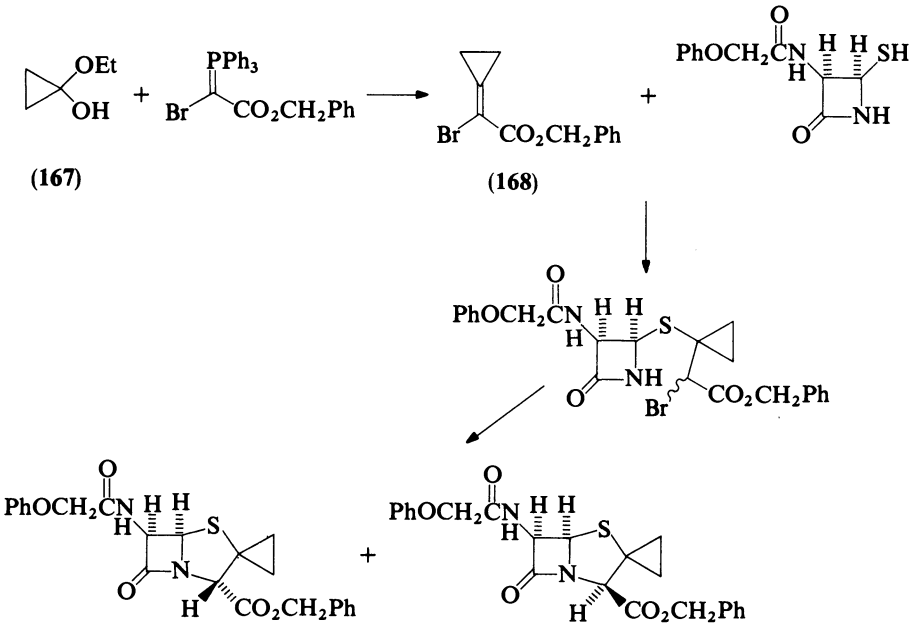
SCHEME 60

cyanohydrin (**162**) as a starting material. Conversion to the ketal (**163**) was accomplished with ethyl vinyl ether, and this was then reduced to the aldehyde (**164**). After conversion of **164** to the amino nitrile, hydrolysis furnished the acid (**165**) as outlined in Scheme 61. Deprotection of **165** was accomplished in acid, yielding DL-cleonine (**166**).



SCHEME 61

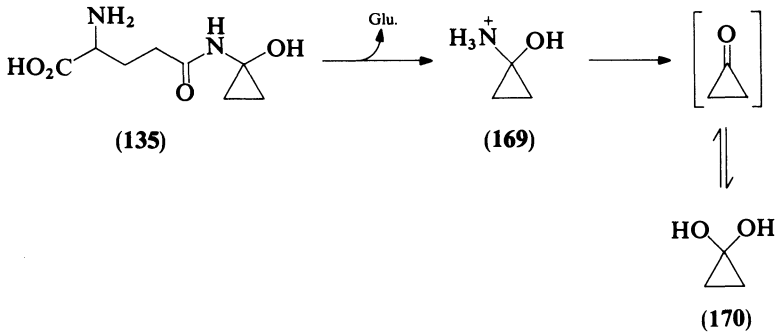
Cyclopropanone ethyl hemiketal (**167**) has also been used in the synthesis of cyclopropanespiro-2-bis-norpenicillanic acids[166], novel analogs of the natural penicillins. In this case, the use of cyclopropanone in a Wittig coupling reaction was nicely illustrated. The intermediate (**168**) was generated in this process and then carried on to the β-lactam derivative as illustrated in Scheme 62.



SCHEME 62

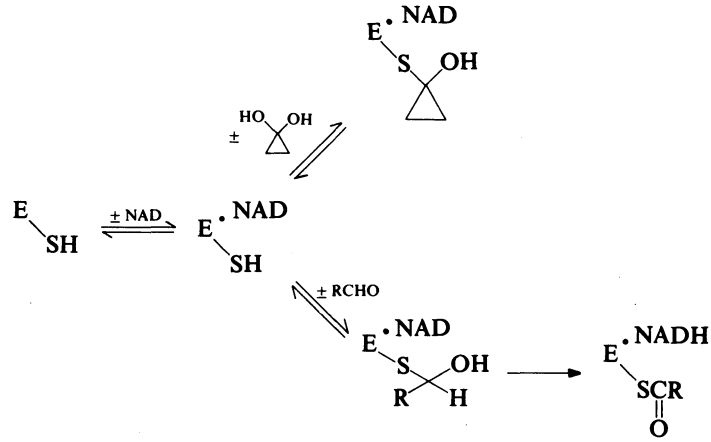
IX. BIOLOGICAL ASPECTS OF CYCLOPROPANONE CHEMISTRY

Coprine, isolated from the *Coprinus atramentarius* mushroom, and identified as N^5-(1-hydroxycyclopropyl)-L-glutamine[154], **135**, is the first example of a natural product containing a cyclopropanone equivalent. Coprine inhibits mouse liver aldehyde dehydrogenase *in vivo* but not *in vitro*[167, 168]. Cyclopropanone hydrate (**170**), which can be derived from coprine by hydrolysis to **169** (equation 39), inhibits the enzyme both *in vivo* and *in vitro*. Cyclopropanone hydrate has thus been proposed as a metabolite of coprine which is the active agent causing the toxic effects[169].



(39)

Cyclopropanone hydrate has been reported to be a potent but reversible inhibitor of a number of enzymes which are sensitive to thiol reagents[169, 170]. The kinetics of inhibition of aldehyde dehydrogenase have been studied in detail by Wiseman and coworkers and the mechanism shown in Scheme 63 has been proposed for the inhibition[170].



SCHEME 63

Cyclopropanone hydrate forms a stable thiohemiketal with the active-site thiol which is not oxidized by nicotinamide adenine dinucleotide (NAD). This hydrate has also been found to be a suicide inhibitor for horseradish peroxidase[171], flavoenzyme alcohol oxidase[172] and quinoprotein alcohol dehydrogenases[173].

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CHAPTER 24

Cyclopropenyl compounds

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I. INTRODUCTION

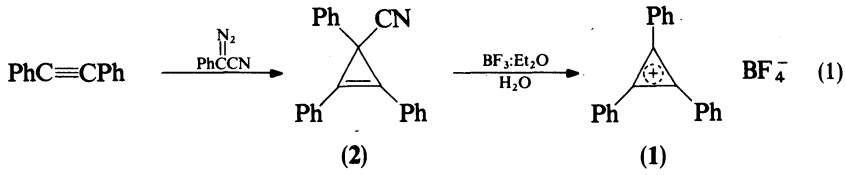
Although the term aromaticity was synonymous with benzene and benzenoid compounds from the Kekule era well into this century, several workers realized that a number of compounds that do not contain benzene rings possess electron configurations which appear to confer the special kind of stability exhibited by the benzene nucleus, and thus appear to have aromatic character. These compounds are termed non-benzenoid aromatics.[1]

The cyclopropenyl ions[2-6], as well as other compounds which incorporate this structural feature by virtue of resonance with an aromatic dipole, occupy an important position in this family. In this chapter our aim is to cover the significant aspects of this group of theoretically important compounds.

II. SYNTHESIS OF CYCLOPROPENYL IONS

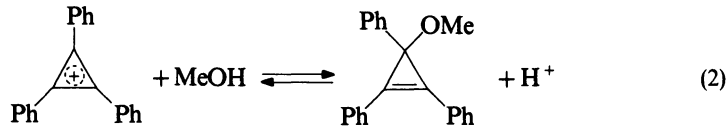
Despite encouragement from early theoretical studies[7], the possibility that cyclopropenyl cation salts might be isolated remained in doubt until 1957 when Breslow reported the

synthesis of the *s*-triphenylcyclopropenyl cation **1** (equation 1)[8]. In this important communication and a subsequent report[9], Breslow was able to show that the starting



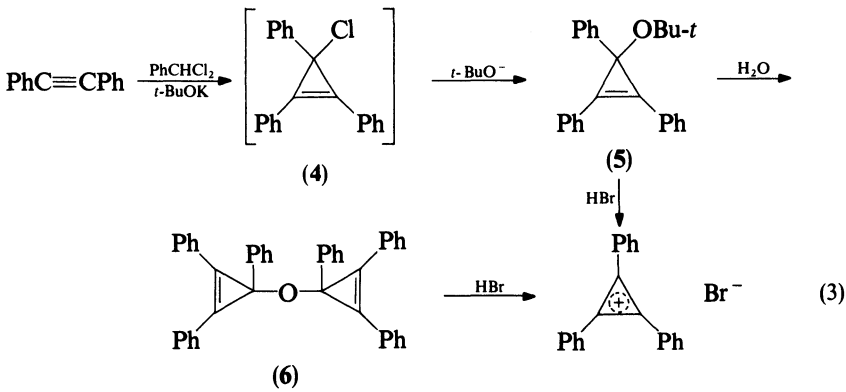
(2) (1) (1)

compound **2** is soluble in non-polar solvents such as benzene and gives no precipitate with ethanolic silver nitrate. It is thus covalent; however, on treatment with boron trifluoride etherate and a trace of water it is converted to the white crystalline salt of cation **1**. Breslow showed that in alcohols, **1** is in reversible equilibrium with ethers, such as **3** (equation 2) and that it is remarkably stable (m. p. 300°C).



(1) (3) (2)

An alternative synthesis of salts of **1**, which proved to be suitable for large scale synthesis, soon followed and is outlined in equation 3[10]. In this approach the carbene is generated by a base-induced reaction, and under the conditions of the reaction the product

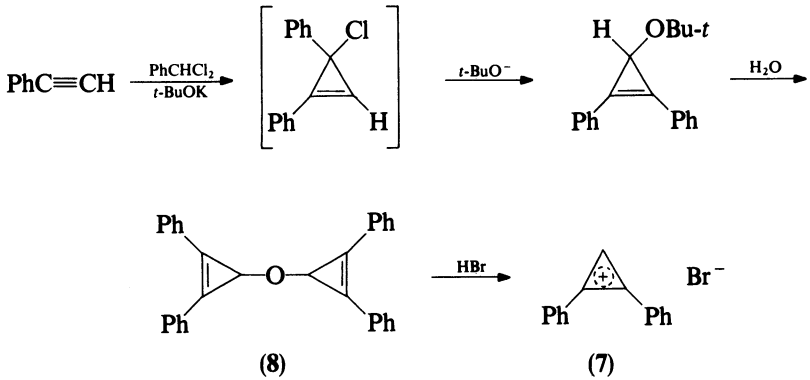


(4) (5) (6)

triphenylcyclopropenyl chloride (**4**) is converted to triphenylcyclopropenyl *t*-butyl ether (**5**). Interestingly, this ether is converted to bis-triphenylcyclopropenyl ether (**6**) during its aqueous washing. Each of these compounds can be converted quantitatively, without isolation, to the bromide of **1** by treatment with hydrogen bromide.

Using this scheme with other diarylacetylenes, or with *p*-methoxybenzyl chloride instead of benzal chloride, the *p*-anisyldiphenyl- di-*p*-anisylphenyl- and tri-*p*-anisylcyclopropenyl ions could be prepared. Monophenylacetylene is also a suitable component for the reaction and diphenylcyclopropenyl bromide (**7**) has been synthesized

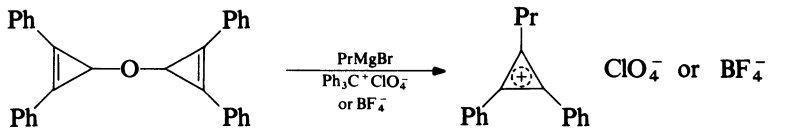
using this procedure (equation 4)[11]. In this case, however, it was necessary to isolate the final ether product (**8**), since the crude reaction mixture did not give a satisfactorily pure cation.



(4)

(**8**) (**7**)

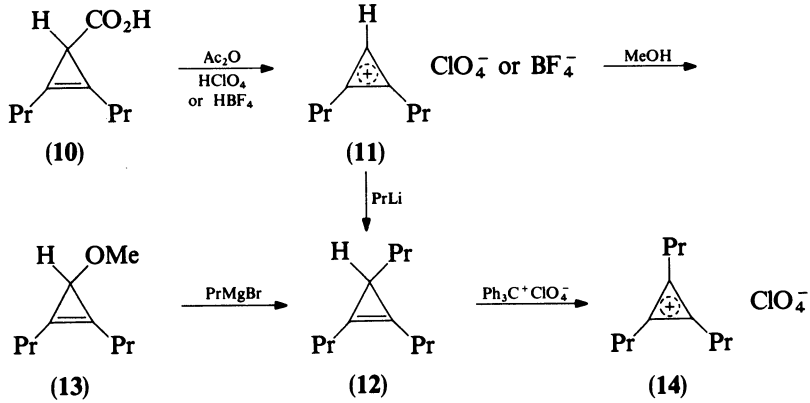
The ether **8** has also been used to prepare *n*-propyldiphenylcyclopropenyl cation **9** as either the perchlorate or fluoroborate by reaction with *n*-propylmagnesium bromide and subsequent hydride abstraction of the resulting impure 3-*n*-propyldiphenylcyclopropene with triphenylmethyl cation (equation 5).



(5)

(**8**) (**9**)

The remarkable properties of these triaryl- and diarylcyclopropenyl ions strongly supported the idea that these cations are fundamental aromatic systems and that the synthesis of derivatives free of phenyl groups should be possible. Indeed, it was soon shown that stable cations bearing only simple alkyl groups could be prepared. For



(6)

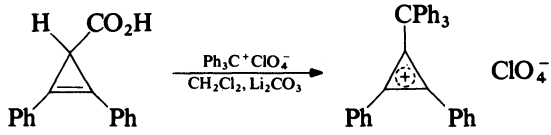
(**10**) (**11**) (**13**) (**12**) (**14**)

example, oxidation of di-*n*-propylcyclopropenecarboxylic acid (**10**) with acetyl perchlorate in acetic anhydride led to di-*n*-propylcyclopropenyl perchlorate (**11**)[12, 13] (equation 6).

The fluoroborate of **11** could be prepared from the perchlorate or directly from the cyclopropene **10**. This ion was used to synthesize tri-*n*-propylcyclopropene (**12**), either by direct reaction with *n*-propyllithium or by conversion of the cation to di-*n*-propylcyclopropenyl methyl ether (**13**) and reaction of this compound with *n*-propylmagnesium bromide. The cyclopropene was converted directly to the ion **14** with triphenylmethyl perchlorate (equation 6).

The subsequent development of other synthetically useful routes to alkoxycyclopropenes has provided ready access to the cyclopropenyl cations using trityl perchlorate or fluoroborate as hydride abstracting reagents[14]. Dichlorodicyanoquinone has also been used for this purpose[15, 16].

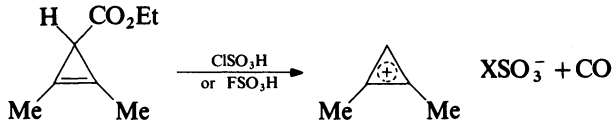
1,2-Diphenylcyclopropenecarboxylic acid gives the corresponding diphenylcyclopropenyl cation using acetyl perchlorate[17]; however, the major product is durene[18] when the tetrafluoroborate salt is used. With triphenylmethyl perchlorate in methylene chloride and lithium carbonate this acid is converted into 1,2-diphenyl-3-triphenylmethylcyclopropenyl cation (**15**)[19] (equation 7).



(7)

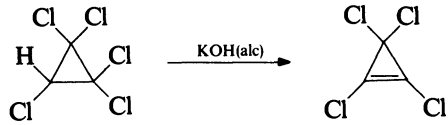
(**15**)

Other simple alkyl or dialkylcyclopropenyl cations have been prepared from cyclopropenecarboxylic esters as outlined in equation 8[20].



(8)

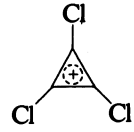
Tetrachlorocyclopropene (**16**), which is readily available from dehydrochlorination of **17**[21] (equation 9) can be treated with strong Lewis acids to yield stable salts of the



(9)

(**17**) (**16**)

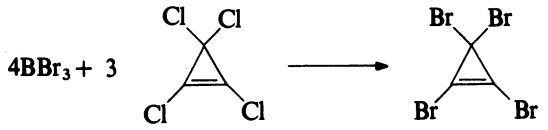
trichlorocyclopropenyl ion **18**[22], or to cyclopropene products which can most reasonably be explained by assuming the intermediate formation of this ion[23]. Thus, gentle warming of a mixture of $AlCl_3$ and excess tetrachlorocyclopropene initiates an exothermic reaction which results in the formation of a white powder identified as the tetrachloroaluminate of **18**. Similarly, treatment of tetrachlorocyclopropene with excess liquid $SbCl_5$ yields on



(18)

workup the hexachloroantimonate. Quenching of either of these salts in water regenerates the cyclopropene.

When BBr_3 is added to tetrachlorocyclopropene, no stable salt precipitates, but the reaction proceeds smoothly to tetrabromocyclopropene **19** (equation 10). This result can



$4BBr_3 + 3$ (16) (19) $+ 4BCl_3$ (10)

be best explained by assuming the intermediate formation of mixed bromochlorocyclopropenyl ions. Fluorinated cyclopropenes have also been prepared from **18** using potassium fluoride in tetramethylene sulfone[23].

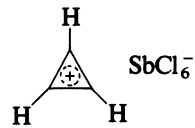
This discovery represented an important advance in the synthesis of cyclopropenyl ions, since **18** can serve as a point of departure in the synthesis of a large variety of new cyclopropenyl salts by reaction with nucleophiles. This is discussed in the subsequent section of this chapter. The conversion of cyclopropenones to cyclopropenyl salts is similarly reserved for a later section.

The synthesis and properties of the parent cyclopropenyl cation itself were reported in 1967[24]. A major hurdle in the synthesis of this species involved the preparation of the precursor 3-chlorocyclopropene (**20**). Under appropriate conditions this compound can

(20)

be isolated from the mixture of mono- and dichlorocyclopropenes that result from the reduction of tetrachlorocyclopropene with tri-*n*-butyltin hydride[25].

On mixing solutions of **20** and $SbCl_5$ in methylene chloride, the cyclopropenyl hexachloroantimonate **21** precipitates as a white solid in quantitative yield[26]. The fact that



(21)

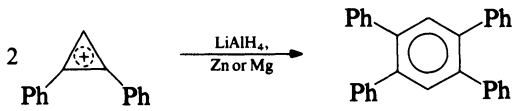
a salt of **21** can be prepared under such mild conditions is further evidence for the aromatic character of this system.

III. CHEMICAL TRANSFORMATIONS OF CYCLOPROPENYL IONS

The chemistry of cyclopropenyl ions is dominated by reactions which lead to cyclopropenes, usually either by reduction or by their reactions with nucleophiles. For example, triphenylcyclopropenyl cations, as well as some other derivatives, can be reduced in good yield to the corresponding cyclopropene using lithium aluminum hydride (equation 11)[27, 28]; however, diphenylcyclopropene which is produced in the analogous reduction of

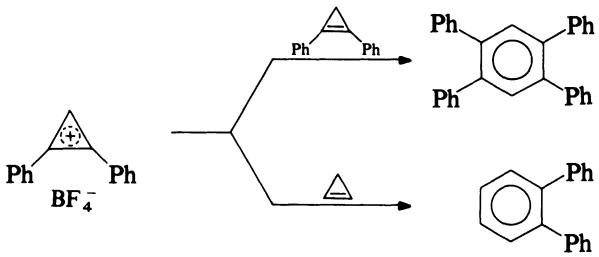
(11)

diphenylcyclopropenyl salts appears to be sufficiently reactive to be intercepted by unreacted cation yielding 1,2,4,5-tetraphenylbenzene (equation 12). The observation that



(12)

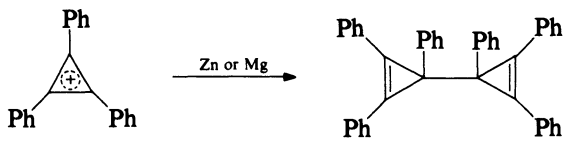
both diphenylcyclopropene and cyclopropene react with diphenylcyclopropenyl fluoroborate in the reactions of equation 13 supports the hypothesis that diphenylcyclopropene is formed in the reduction[28, 29].



(13)

Reduction of these ions using sodium borohydride with inverse addition so that the cation is never present in high concentration yields the respective cyclopropene in high yield[29]. Dialkylcyclopropenyl salts can also be reduced using this procedure. In each case the cyclopropene with the more highly substituted double bond is produced[30].

Reduction of triphenylcyclopropenyl salts with other reagents including Mg and Zn have been reported. Reduction of triphenylcyclopropenyl cations by these metals yields **22** (equation 14), whereas the diphenyl species yield tetraphenylbenzene (equation 12)[31, 32]. Isolation of bis-cyclopropenes has also been reported from reductions using chromium(II)



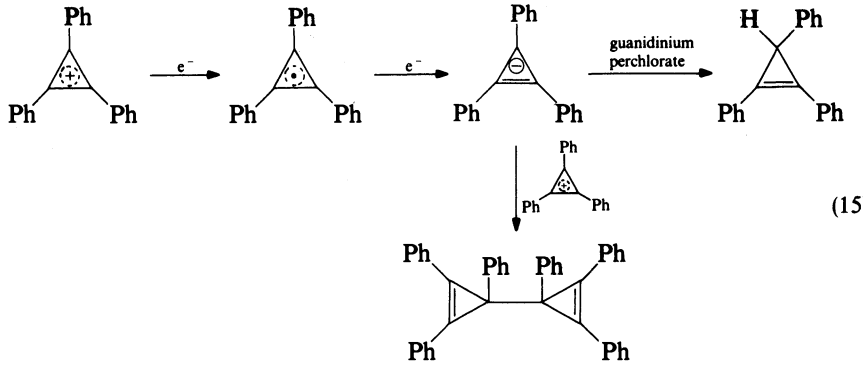
(14)

(22)

reagents[33]. Curiously, *n*-propyl-substituted cyclopropenyl cations fail to react with this reagent. These reductions are assumed to proceed via cyclopropenyl radicals.

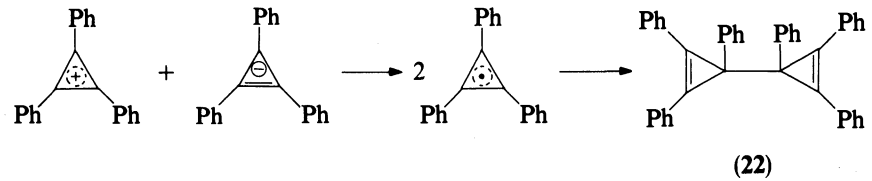
The formation of hexaphenylbenzene from the photolysis of triphenylcyclopropenyl salts can also be rationalized in terms of triphenylcyclopropenyl radicals which dimerize and then rearrange to the hexaphenylbenzene[34, 35].

Extensive studies have been carried out on the electrochemical reduction of the triphenylcyclopropenyl cations[36–39]. These reactions are presumed to proceed via the route outlined in equation 15. Although the bis-cyclopropene **22** is the major product,



(15)

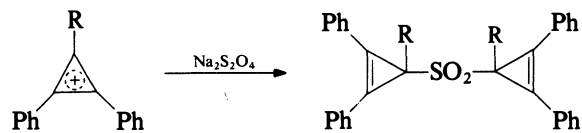
the use of guanidinium perchlorate as a supporting electrolyte did lead to some protonation of the anion. It has been suggested that the dimer results from the combination of two radicals (equation 16) since capture of the anion by the cyclopropenyl



(16)

cation was much more effective than capture by protonation even when the guanidinium cation was present in excess.

Reduction of either triphenyl- or diphenylcyclopropenyl salts with sodium dithionite leads to the formation of bis-(cyclopropenyl)sulfones[40] (equation 17).

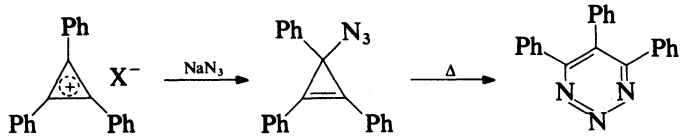


(17)

R = Ph or H

It is not surprising that cyclopropenyl ions react with a large variety of nucleophiles. The reversible equilibrium with ethers in alcohols has been discussed earlier.

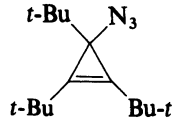
Even the carbon–azide linkage, normally a model for covalency, takes on ionic character in these compounds[40,41]. Thus, sodium azide reacts with salts of **1** to yield the azidocyclopropene (**23**) which rearranges upon heating to the triazine (**24**) (equation 18).



(18)

(**23**) (**24**)

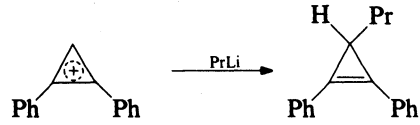
This rearrangement is preceded by a degenerate rearrangement in the cyclopropene in which the azide group exchanges sites. In this regard the nuclear magnetic resonance



(**25**)′

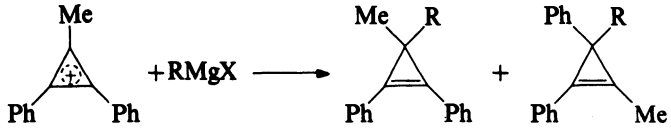
spectrum of the azidocyclopropene (**25**) shows two types of *t*-butyl groups at low temperature, but only a single one at or near room temperature[42].

Cyclopropenyl cations can be reacted with Grignard reagents[27,43,44] or lithium alkyls[13] to yield cyclopropenes (equation 19). The disubstituted cyclopropenyl salts



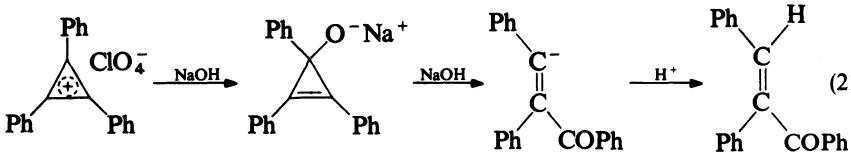
(19)

usually react at the unsubstituted position, whereas trisubstituted salts appear to react randomly, e.g. equation 20.



(20)

The cyclopropene produced upon reaction of the triphenylcyclopropenyl cation with aqueous alkali collapses to give the ring-opened product **26**[45] (equation 21). D'yakonov and coworkers[45] have used this reaction to confirm the symmetry of the cation by labeling

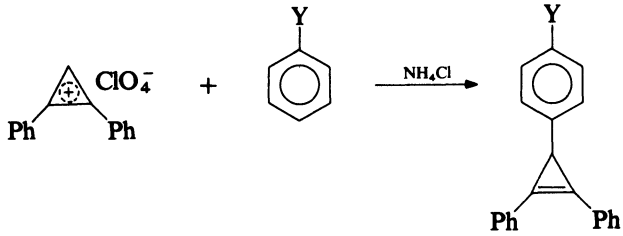


(21)

(**26**)

one of the ring carbons with ^{13}C. The resulting product was shown to have the three sites equally labeled.

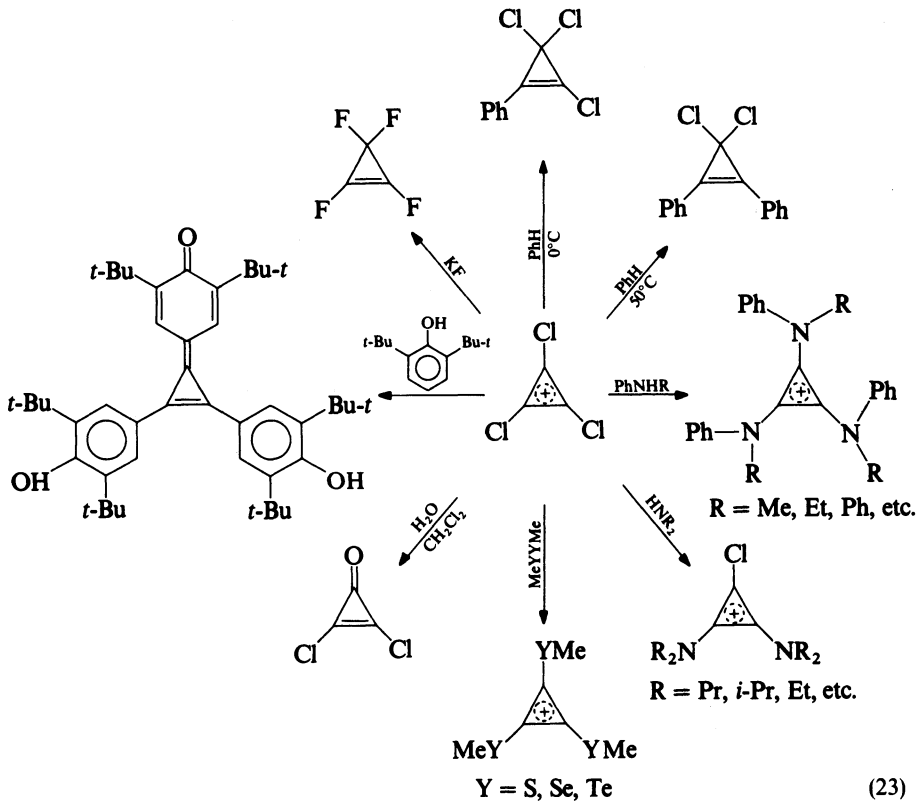
Benzene derivatives with strongly activating substituents (NR_2, OR) react at the *para* position to yield cyclopropenes[46–48] (equation 22).



(22)

Y = NMe_2, OMe

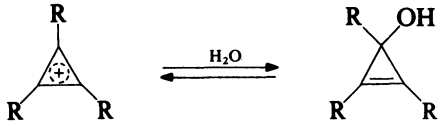
Since halogen attached to a cyclopropenyl ion can be displaced by a large number of nucleophiles, the trichlorocyclopropenyl cation **18** serves as a precursor, *par excellence*, for heterosubstituted cyclopropenyl cations, or cyclopropenes. A few of these are outlined in equation 23 without comment. The reader is referred to the review by Yoshida[2] for a more detailed account of this area.



(23)

IV. OTHER PROPERTIES OF CYCLOPROPENYL IONS

Although many of the substituted cyclopropenyl ions are marvels of stability, salts of the parent ion darken rather rapidly on heating and exposure to atmospheric moisture causes rapid decomposition. The hexachloroantimonate salt is stable for a long period at $-20°C$ and for a few hours at room temperature. As might be expected, the cyclopropenyl salts are soluble in polar solvents such as acetonitrile and dimethylformamide, but are insoluble in non-polar solvents. They, of course, react with protic solvents as described earlier. In aqueous solution the equilibrium of equation 24 is established. The pH required to



(24)

establish a 1:1 equilibrium for this ionization can be taken as a measure of the stability of the cation and is designated pK_{R^+}. This important thermodynamic property has been determined to be 7.4 ± 0.1 for the parent cation[13]. This value indicates that this ion is more stable than the allyl cation by ~ 18 kcal mol^{-1}.

The pK_{R^+} values of a large number of cyclopropenyl ions have been determined Surprisingly, these values show that alkyl groups stabilize the cations more than phenyl groups. Furthermore, the values reported for several trialkylcyclopropenyl salts indicate the order of stability to be methyl > *n*-propyl > isopropyl $\approx$ *t*-butyl[13]. This order of stabilities would seem to indicate that the cyclopropenyl ions are less susceptible to stabilization by conjugative electron donation than open shell carbocations. One possible explanation for this order of stabilities is steric crowding in the cation which would be lessened when the alcohol is formed, eliminating some of the eclipsing interactions. The trend observed in another investigation[49] where a larger number of substituents was studied shows $R_2N \gg c\text{-}C_3H_5 > OEt > n\text{-}Pr \approx SMe > Ph > H$, indicating conjugative effects to still be the dominating factor in stabilizing these cations, though less so than with most cations.

The special effect of cyclopropyl[50,51] is noteworthy since the tricyclopropyl–cyclopropenyl cation, the most stable of all the hydrocarbon cyclopropenyl cations, is nearly as stable as cations stabilized by complexation with organometallic reagents. The triferrocenyl[52] and tri(3-guaiazulenyl)cyclopropenyl ions[53] can be cited as examples since these species have pK_{R^+} values greater than 10. Other metal complexed cyclopropenyl species have also been reported[54–57].

Spectral properties of the cyclopropenyl ions are all consistent with a fully delocalized structure[20,25]. The cyclopropenyl ion itself exhibits a strongly deshielded singlet at δ 11.0 resulting from both hybridization effects and the positive charge. The large ^{13}C–H coupling constant of 235 Hz corresponds to sp hybridization at the carbon. The infrared spectrum of both the hexachloroantimonate and the tetrachloroaluminate show four bands at 3105, 1276, 908 and 736 cm^{-1} for the cation. The observation of four bands in the infrared spectrum is expected for a symmetrical, delocalized structure of the cation with D_{3h} symmetry.

A hybridization scheme for the cyclopropenyl cation which is consistent with these spectral features is illustrated in Figure 1.

X-ray crystallographic data for triphenylcyclopropenyl perchlorate[58,59] as well as other compounds[60] confirm the symmetry of the three-membered ring.

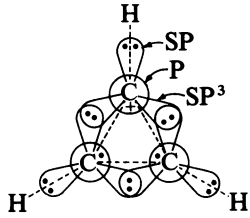
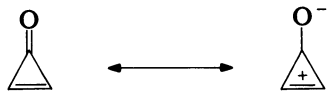


FIGURE 1 A hybridization scheme for cyclopropenyl cation

V. SYNTHESIS OF CYCLOPROPENONES

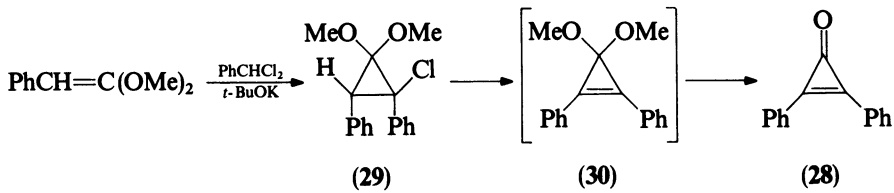
Cyclopropenone (**27**) and its derivatives are expected to share some of the aromatic stability of the cyclopropenyl cations, to which they are related by structure **27a**. It is not



(**27**) (**27a**)

surprising then that the successful synthesis of cyclopropenyl cations (and thus the experimental confirmation of LCAO-MO theory that the cations would possess a delocalized system of $(4n+2)$ π electrons) stimulated efforts to prepare the cyclopropenones[61, 62].

The first cyclopropenone, diphenylcyclopropenone (**28**), was reported in 1959[63]. This, the most common of the cyclopropenones, was prepared by the reaction of phenylketene dimethylacetal with benzal chloride and potassium *t*-butoxide. The chlorocyclopropenone ketal (**29**) which is produced from these reagents via phenyl(chloro)carbene addition to the ketal undergoes β-elimination yielding **30** which can be hydrolyzed, *in situ*, to give the cyclopropenone (equation 25). A series of arylphenylcyclopropenones were prepared using this method[64].



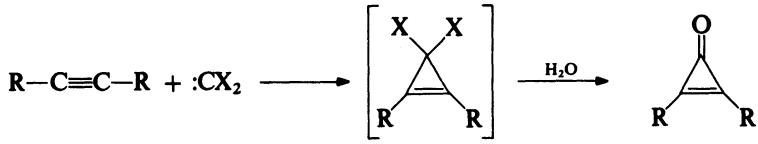
(**29**) (**30**) (**28**)

(25)

Several workers have subsequently noted that diphenylcyclopropenone is a powerful vesicant[65, 66] and that a single exposure may cause hypersensitivity[67].

Another route, developed independently by Volpin and coworkers[68], also relies on hydrolysis of cyclopropene intermediates and is illustrated in equation 26.

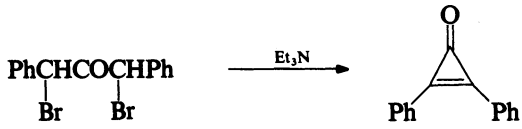
The scope of this process is evident from extensive studies which have shown that the dihalocarbene can be generated from most of the usual precursors by using the phase transfer method[69]. The reactivity of dihalocarbenes[70–73] and carbenoids[74, 75] towards acetylenes has also been reported.



(26)

R = Ar, alkyl
X = Br, Cl, F

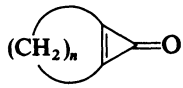
A superior route to many cyclopropenones appears to be the Favorskii-like reaction of α, α′-dibromoketones with tertiary amines or potassium *t*-butoxide (equation 27)[65,76].



(27)

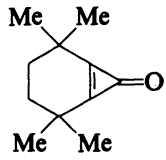
(28)

This method seems to be the one of choice from a preparative standpoint, since the yields are usually high (40–60 %), the procedure can be adapted to large-scale synthesis and a wide variety of cyclopropenones[77–81] including bicyclic derivatives **31a**[82] and **31b**[83] can be prepared.



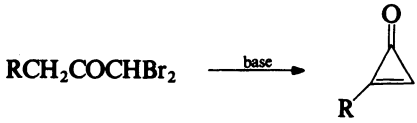
(31a)

$n = 5, 9$



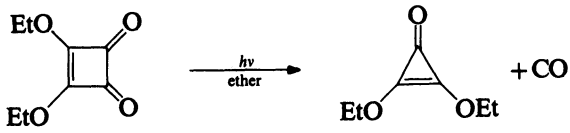
(31b)

A variation of the method uses geminal α-dibromoketones as a route to monoalkylcyclopropenones (equation 28)[84].



(28)

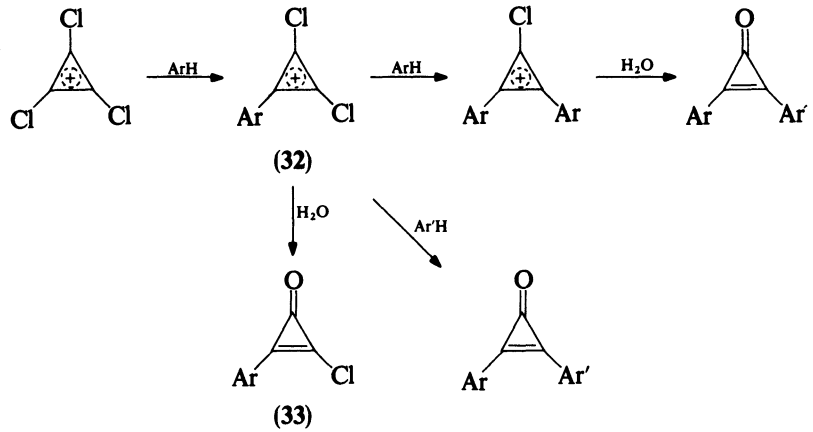
Other less general methods that have been reported include the extrusion of carbon monoxide from cyclobutenediones (equation 29)[85] and the photolytic or Ag_2O-induced decomposition of α, α′-bisdiazodibenzyl ketone[86]. Diphenylcyclopropenone has been



(29)

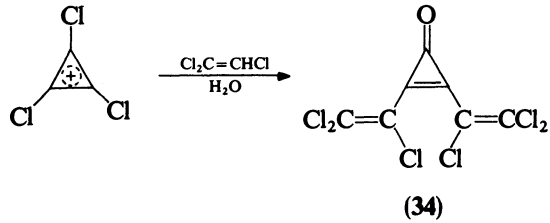
prepared this way, but the process is complicated by numerous side reactions including secondary reactions of the cyclopropenone and a competitive Wolff rearrangement of the initially produced carbene.

Tetrachlorocyclopropene in the presence of Lewis acids or the trichlorocyclopropenyl cation are important starting materials in cyclopropenone syntheses[87–91]. In this method the cyclopropene or salt is reacted with benzene or derivatives of benzene bearing functional groups such as alkyl, alkoxy, hydroxy, or halogen to yield diaryl-substituted cations. Upon hydrolysis these cations yield the cyclopropenone. In some cases the monoaryl cation (**32**) can be obtained and converted to the aryl chlorocyclopropenone **33**. Alternatively, the monoaryl cation can be reacted with a second aromatic species to give cyclopropenones with different aryl groups (equation 30).



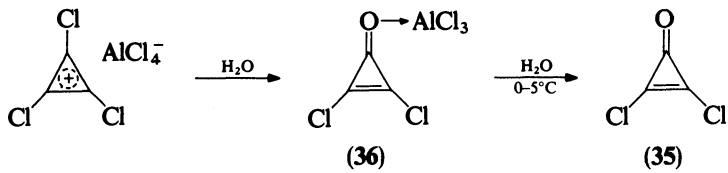
(30)

Compounds such as **34** can also be prepared from vinyl halogen compounds[92] (equation 31).



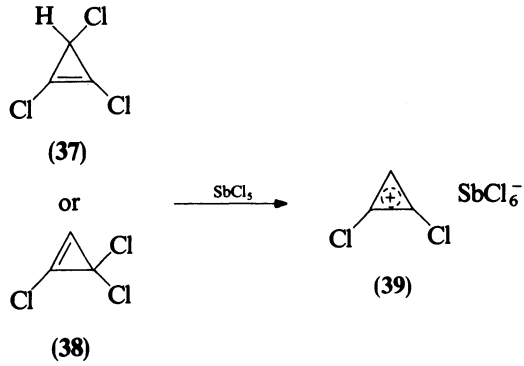
(31)

A special procedure has been devised to synthesize dichlorocyclopropenone (**35**), since this compound cannot be prepared by direct hydrolysis of the cation. This labile compound can, however, be liberated by careful hydrolysis of the $AlCl_3$ adduct **36**[93] (equation 32).



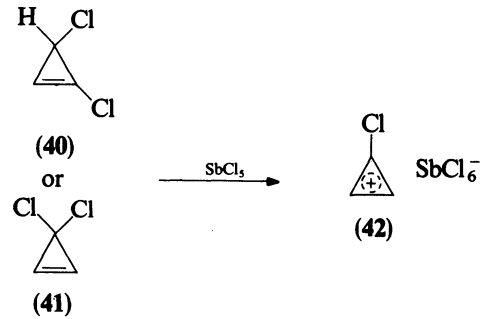
(32)

Unsubstituted cyclopropenone was prepared by hydrolysis of the di- and trichlorocyclopropenes obtained from the reduction of tetrachlorocyclopropene[94–96]. Treatment of the trichlorides **37** and **38** with $SbCl_5$ affords the hexachloroantimonate salt of



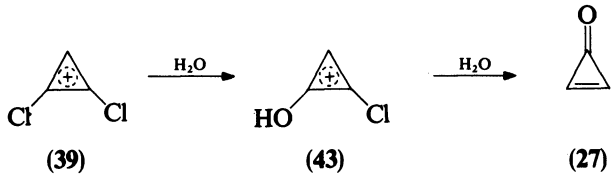
(33)

dichlorocyclopropenyl cation **39** (equation 33). Similarly, the dichlorocyclopropenes **40** and **41** afford the cyclopropenyl cation **42** as its hexachloroantimonate (equation 34).



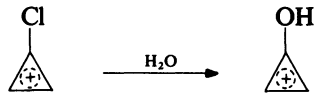
(34)

On treatment with moisture, cations **39** and **42** are converted to new species thought to be the chlorohydroxycyclopropenyl cation **43** (equation 35) and hydroxycyclopropenyl



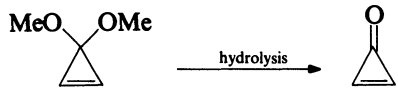
(35)

cation **44** (equation 36), respectively. With further addition of water, **43** is converted to cyclopropenone.



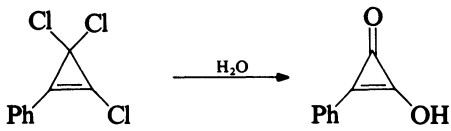
(36)

Hydrolysis of cyclopropene dimethyl acetal (**45**) provides a further useful route to cyclopropenone[97,98] (equation 37).



(**45**) (**27**) (37)

The theoretically interesting compound **46**[6], a strong acid, ($pK_a = 2.0 \pm 0.5$) can be secured by careful hydrolysis of **47** or the ketal[91,99] (equation 38). Surprisingly, cyclohexylcylcopropenone is a naturally occurring compound[164]!



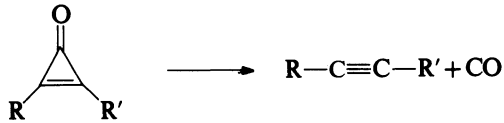
(**47**) (**46**) (38)

The preparation of selected cyclopropenones is summarized in Table 1.

VI. CHEMISTRY OF CYCLOPROPENONES

Due to its ready availability, the chemistry of diphenylcyclopropenone has been investigated more extensively than any of the other cyclopropenones. Nevertheless, the chemistry of a sizeable number of these compounds has now been reported[2,61,62].

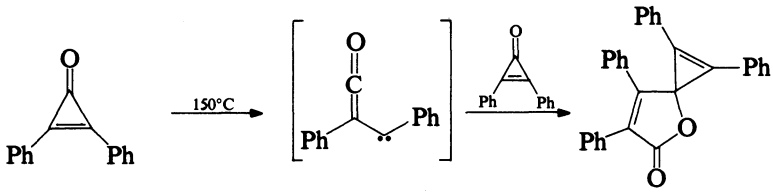
The thermal elimination of carbon monoxide to yield an alkyne (equation 39) takes place readily when cyclopropenones are heated or when subjected to photolysis or electron



(39)

impact[76,100,101]. As expected, the diarylcyclopropenones usually decarbonylate at a lower temperature (~ 150°C) than the dialkyl derivatives (~ 190°C). The unusually high temperature required for these extrusion reactions can be attributed to the requirement that a symmetry-imposed barrier has to be overcome.

At temperatures below the decarbonylation barrier, stable dimers are observed. Thus, thermolysis of diphenylcyclopropenone at 150°C or in refluxing toluene leads to the dimer **48**[76]. The formation of **48** can be rationalized as a dipolar addition of the ring-opened species **49** to the C=O group of a second molecule (equation 40). The codimerization of



(**49**) (**48**) (40)

Table 1. Preparation of selected cyclopropenones

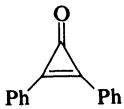
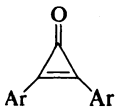
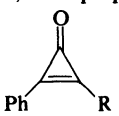
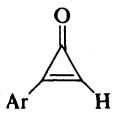
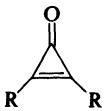
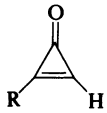
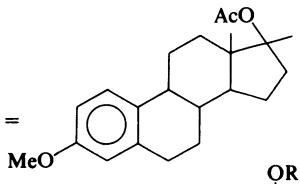
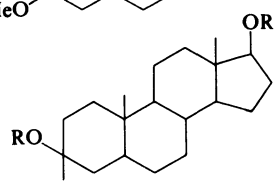
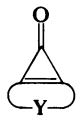
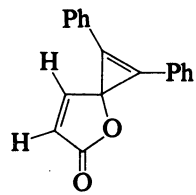
Cyclopropenone	Method[a]	Yield %	Ref.
	From $PhCH{=}C(OMe)_2$	80	76
	From $PhC{\equiv}CPh$	24	76
		63	74
	From $[PhCH(Br)]_2CO$	45	76
	From $[PhCH(Cl)]_2CO$	12	76
			
Ar =			
p-tolyl	C	33	168
p-anisyl	C	73	168
p-*t*-butylphenyl	C	60	77
p-chlorophenyl	C	53	168
p-fluorophenyl	C	49	33
3,5-diisopropyl-4-hydroxyphenyl	C	82	89
			
R =			
Me	A	70	45
Et	A	44	210
t-Bu	A	65	62
$PhCH_2$	A	23	210
1-naphthyl	A	54	62
trans-*β*-styryl	B	10	210
Et_2N	A		82
$PhC{\equiv}C$	B	6	210
OH	C	36	91
Cl	C	20	91
			
Ar =			
Ph	A	33	81
p-anisyl	A	14	62
			
R =			
Me	B	19	100
		12	62
Pr	A	9	82
Bu	B	12	82
t-Bu	A	36	101

Table 1. Continued

Cyclopropenone	Method[a]	Yield %	Ref.
Δ	A	6	49
$CH{=}CMe_2$	—	—	147
$CCl{=}CCl_2$	C	47	92
Cl	—	—	93
OEt	—	10	85
$i\text{-}Pr_2N$	C	80	212
PhS	B	4	210
 R =			
Me	B	20	100
Pr	B	17	100
Pn	A	15	99
R = 	B	59	211
R = 	—	15	211
			
Y = $(-CH_2-)_5$	A	56	82
Y = $(-CH_2-)_9$	A	8	82
Y = $-CMe_2CH_2CH_2CMe_2-$	A	41	83

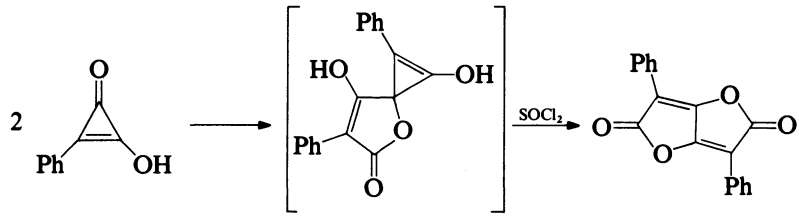
[a] A, Favorskii method; B, dihalocarbene method; C, trichlorocyclopropenyl cation method.

diphenylcyclopropenone with cyclopropenone itself, yielding **50**, has also been reported[102].



(50)

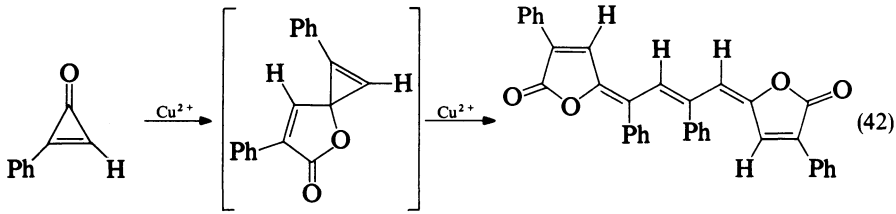
In a number of cases these dimers have been shown to undergo subsequent transformations. The dimer of phenyl hydroxycyclopropenone, compound **51**, yields



(41)

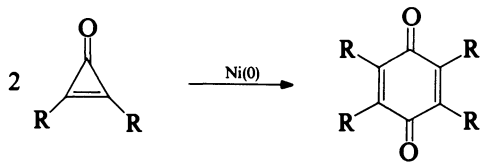
(46) **(51)** **(52)**

lactone **52** on treatment with thionyl chloride[103] (equation 41). A tetramer was observed when phenylcyclopropenone was treated with Cu^{2+} ions[81] (equation 42).



(42)

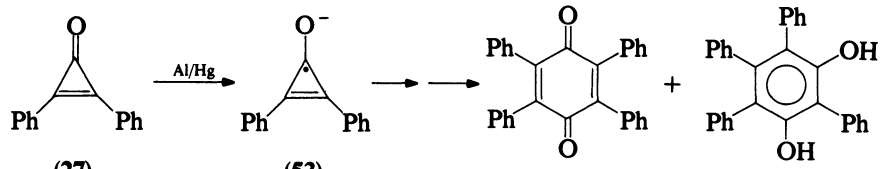
In the presence of Ni(0) compounds, certain cyclopropenones have been shown to yield quinones (equation 43)[104] as well as higher oligomers and trimers[105].



(43)

R = Pr, Ph

Reductive dimerization was observed when **27** was treated with aluminum amalgam[106, 107]. This reaction probably proceeds via the cyclopropenone ketyl **53** (equation 44). A prismane intermediate has been suggested.

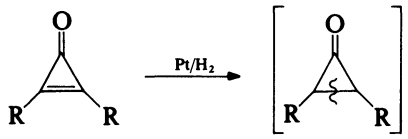


(27) **(53)**

(44)

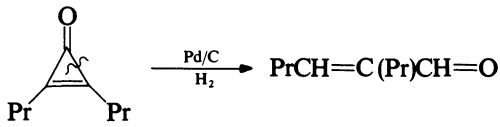
Although catalytic reduction of cyclopropenones can be effected readily, the course of the reaction is sensitive to the catalyst used. Thus, Pt/H_2 gives acyclic ketones resulting

from reductive cleavage of the carbon–carbon bond in the intermediate cyclopropanone (equation 45)[76, 82, 96, 101]. Reduction of *n*-pentyl cyclopropenone[84] using Pd/C followed a



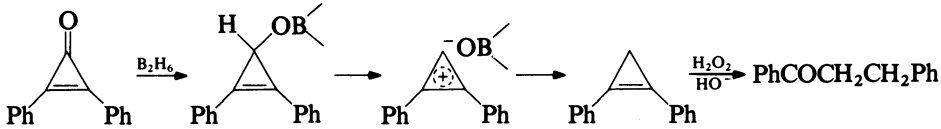
(45)

similar course, whereas di-*n*-propylcyclopropenone gave 2-propyl-2-hex-2-enal (equation 46)[82]. Cyclopropanones could not be detected during these reduction[99].



(46)

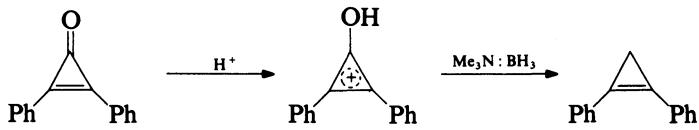
Treatment of diphenylcyclopropenone with diborane followed by alkaline hydrogen peroxide led to the formation of β-phenylpropiophenone (equation 47)[108]. A cyclopro-



(47)

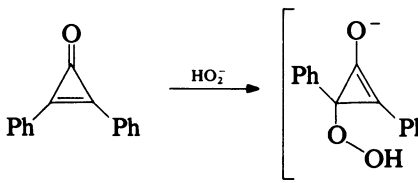
penyl salt has been postulated as an intermediate in this reaction. Lithium aluminum hydride leads to reduction of both double bonds[109].

Selective reduction of the carbonyl group in diphenylcyclopropenone can be achieved indirectly via the cation using trimethylamine:borane[110] (equation 48).



(48)

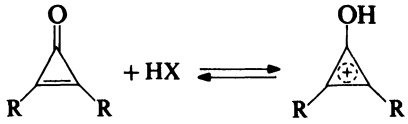
Oxidation of diphenylcyclopropenone with *m*-chloroperbenzoic acid gave a mixture of benzil, diphenylacetylene and benzophenone, whereas di-*t*-butylcyclopropenone gave mainly 4,5-epoxy-2,2,4,5-tetramethylhexan-3-one[111]. Alkaline hydrogen peroxide and diphenylcyclopropenone yield the same products along with benzyl phenyl ketone (equation 49)[112]. The benzyl phenyl ketone is thought to arise from addition of



(49)

hydroperoxy ion to the carbon–carbon double bond followed by loss of carbon dioxide. Oxidation with potassium permanganate gives benzil[113].

Cyclopropenones react readily with most electrophiles. Protonation results in the formation of hydroxycyclopropenyl salts (equation 50)[82, 96, 100]. Alkyl- and cyclopropyl-substituted cyclopropenones are markedly more basic than phenyl-substituted cyclopropenones (or other α, β-unsaturated compounds)[115]. This is emphasized by the observation that di-*n*-propylcyclopropenone can be extracted from 12 N HCl whereas diphenylcyclo-

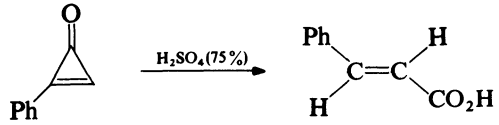


(50)

$X = BF_4^-, ClO_4^-, HSO_4^-$

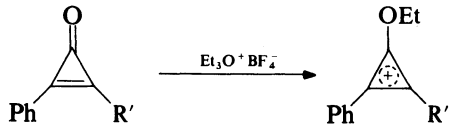
propenone cannot[114]. This effect can be attributed to the greater stabilization of the protonated species by the electron-donating alkyl groups and parallels the observation that cyclopropenyl ions have larger pK_{R^+} values than the aryl-substituted cations. The pK of cyclopropenone itself is -5.2 ± 0.3[96].

In a few cases ring-opened products are observed[81, 83, 93], i.e. equation 51.



(51)

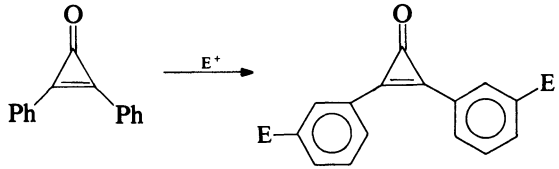
Alkylation on oxygen has been observed when either phenyl-[81] or diphenylcyclopropenone[76] is treated with triethyloxonium tetrafluoroborate (equation 52).



(52)

R′ = Ph or H

Diphenylcyclopropenone has been brominated using *N*-bromosuccinimide in aqueous sulfuric acid to give a product in which both phenyl groups are brominated at the *meta* position[116]. A similar reaction was observed when the cyclopropenone was subjected to nitration (equation 53)[117].

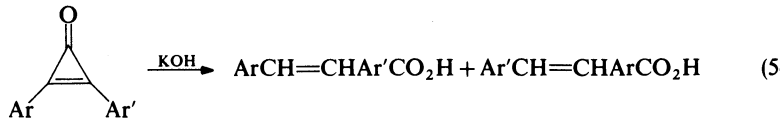


(53)

E = NO_2, Br

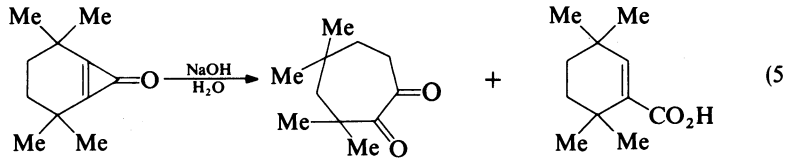
The reactions of cyclopropenones with nucleophiles have been investigated extensively, with products arising from either conjugate addition or addition to the carbonyl group

having been observed[62,118-120]. In some cases ring-opening reaction occur upon treatment of the cyclopropenone with aqueous alkali. Diarylcyclopropenones are cleaved readily as illustrated in equation 54[64]. Most dialkylcyclopropenones react less readily[114]



(54)

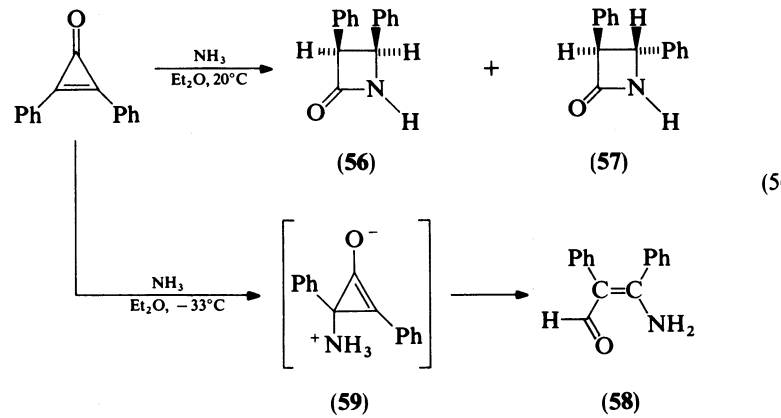
and di-*t*-butylcyclopropenone reacts very slowly[101]. As expected, the strained bicyclic cyclopropenones, such as **31b**, are the most reactive (equation 55)[121].



(55)

(31b) **(54)** **(55)**

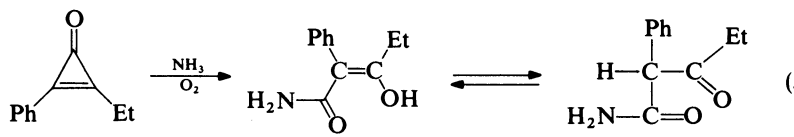
The reaction of amines with cyclopropenones appears to be extremely sensitive to the reaction conditions[120,122]. Ammonia reacts with diphenylcyclopropenone at room temperature to yield the isomeric *β*-lactams **56** and **57**, whereas the vinyl aldehyde **58** is produced at −33°C. These results can be rationalized in terms of the intermediate **59** which would result from conjugate addition of the nucleophile at carbon (equation 56).



(56)

(56) **(57)** **(59)** **(58)**

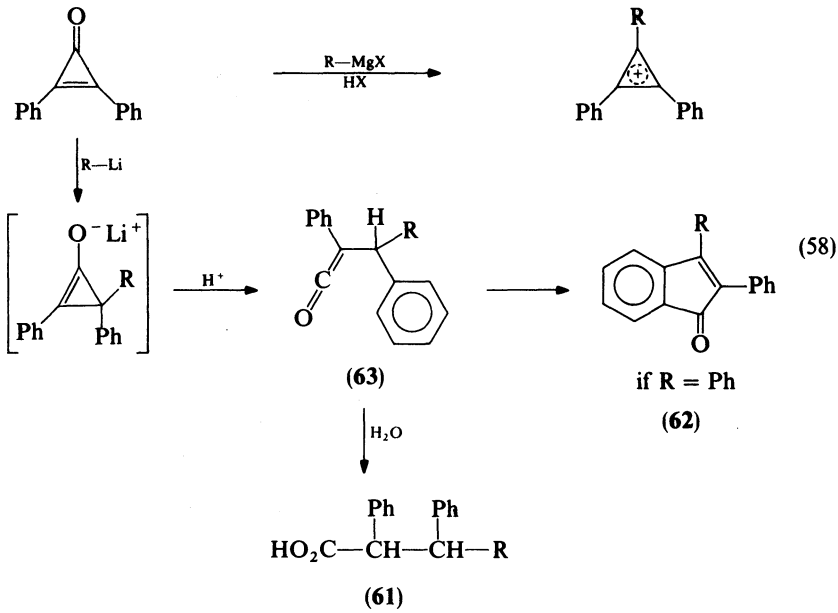
Ethyl phenyl cyclopropenone, on the other hand, experiences addition at the carbonyl carbon yielding the *β*-keto amide **60** (equation 57)[121]



(57)

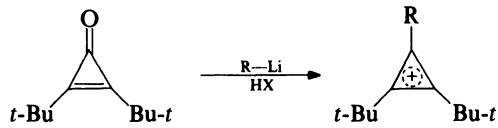
(60)

Organometallic reagents react with cyclopropenones either by conjugate addition or at the carbonyl carbon. Thus, Grignard reagents add to diphenylcyclopropenone to yield the corresponding cyclopropenyl cation[49, 76]; however, organolithium reagents add to the same compound to yield products which appear to be derived from conjugate additions as indicated by products **61** and **62**[123]. The ketene **63** is assumed to be an intermediate in this reaction (equation 58). The ketene can be intercepted with water to yield **61** or undergo



(58)

intramolecular acylation to yield **62**. In contrast, di-*t*-butylcyclopropenone yields the cation with organolithium reagents (equation 59)[101].

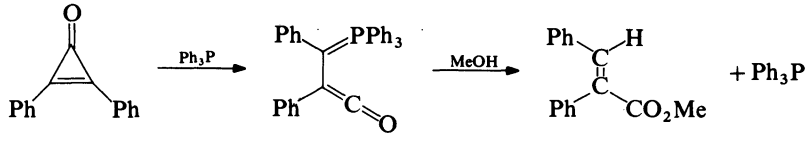


(59)

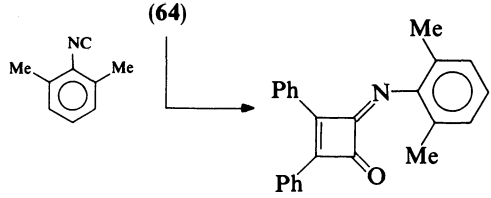
Phosphorane (**64**) can be isolated in pure form when diphenylcyclopropenone is treated with triphenylphosphine[124]. This product arises, at least formally, by interception of the ring-opened species **49** by the phosphine. It can be decomposed by methanol to methyl α-phenylcinnamate and triphenylphosphine. Isocyanides such as 2,6-dimethylphenyl isocyanide react with **64** to yield the interesting product **65**, an imine of cyclobutenedione (equation 60)[125].

Pyridinium, phosphonium, arsonium and sulfonium acyl ylides all react with diphenylcyclopropenone to give 3,4-diphenyl-α-pyrones (equation 61)[126–131]. These reactions are assumed to be initiated by attack of the acyl oxygen on the cyclopropenone.

A variety of carbonyl group derivatives of cyclopropenones have been reported. The reaction of diphenylcyclopropenone with phosphorus pentasulfide gives diphenylcyclopropenethione (equation 62)[32, 208]. The thione has also been prepared using thioacetic acid

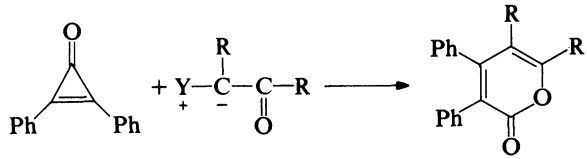


(64)



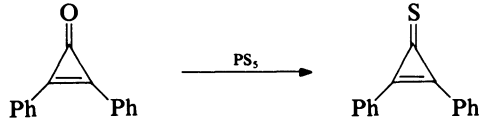
(60)

(65)



(61)

$Y = R'_2S,\ R'_3P,\ R'_3As,\ C_5H_5N$

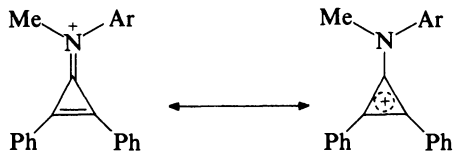


(62)

(66)

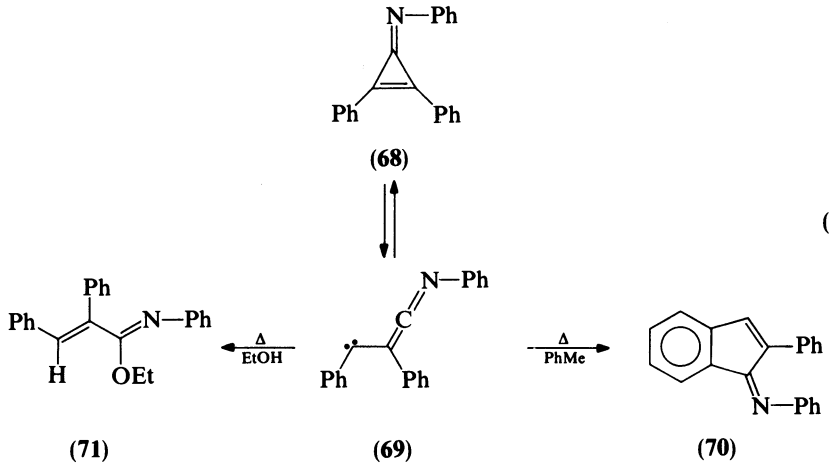
in the presence of tetrafluoroboric acid or perchloric acid[133,134]. An X-ray crystal structure of **66** shows little contribution from a dipolar structure[135].

Cyclopropenyl imminium salts can be prepared by the reaction of cyclopropenones with substituted ammonium salts[136] or by the reaction of ethoxycyclopropenyl salts with amines[137]. The ease of rotation about the carbon-nitrogen double bond shows that the positive charge is not located solely on the nitrogen as in **67** but is shared with the cyclopropene ring as in **67a**[136].



(67) (67a)

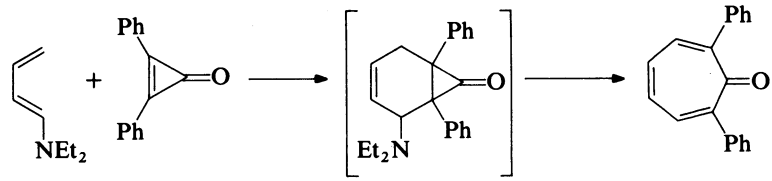
When the free imine **68** is heated, the ring-opened dipolar intermediate **69** is formed[138]. The fate of this species depends on the solvent; in aprotic solvents an indene derivative (**70**)



(63)

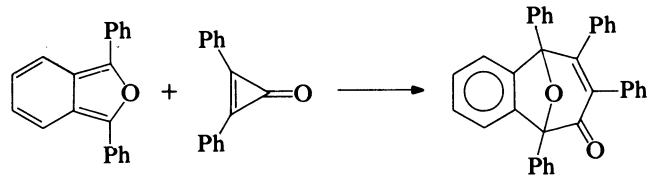
is formed, whereas protic solvents such as ethanol yield enamine **71** (equation 63).

Substituted cyclopropenones such as the diphenyl derivative undergo cycloaddition reactions with activated dienes either by [4+2] or [4+3] modes. For example, *N*-1,3-butadienyl-*N*,*N*-diethylamine adds to diphenylcyclopropenone via the normal [4+2]



(64)

mode, followed by elimination of diethylamine to yield 2,7-diphenyltropone (equation 64)[139]. Diphenylisobenzofuran, on the other hand, follows the abnormal [4+3] route yielding **72** (equation 65)[140].

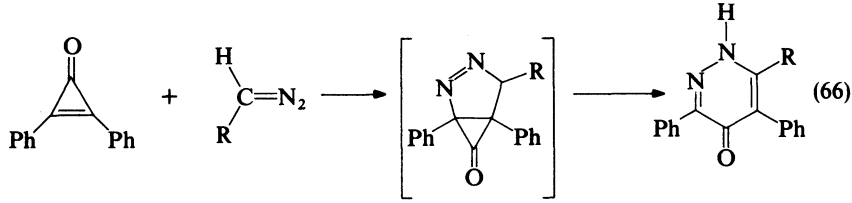


(65)

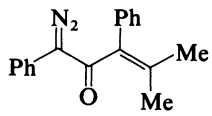
(72)

Fairly extensive studies have been reported on the reactions of enamines and other electron-rich multiple bonds with cyclopropenones. The reader is referred to the excellent review of Eicher and Weber for an exhaustive discussion of this area[62].

Several diazoalkanes have been shown to add as 1,3-dipoles to cyclopropenones. Diazomethane, diazoethane and diazopropane all add in this way to diphenylcyclopropenone to give the corresponding 3,5-diphenyl-4-pyridazinones (equation 66)[76]. An exception is 2-diazopropane which yields the diazoketone **73**[141].



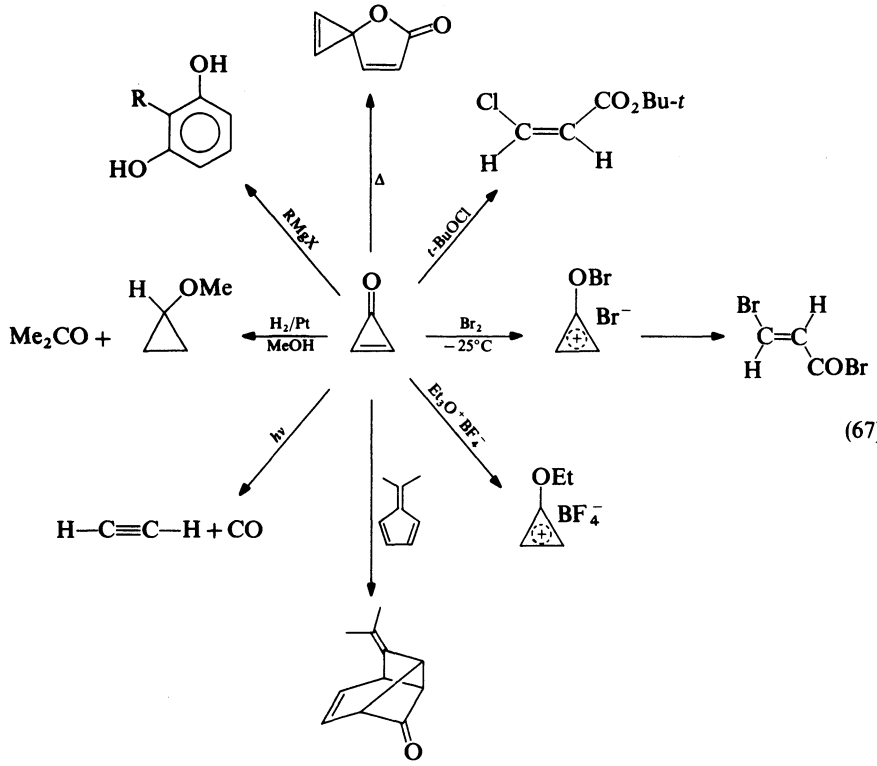
(66)



(73)

Cyclopropenone itself seems to exhibit its own unique chemistry. The compound can be kept at its melting point ($\sim -28°C$) for several weeks but polymerizes rapidly at room temperature. It is stable in organic solvents at room temperature. In aqueous solution no hydration can be detected by infrared spectroscopy.

The reactions of cyclopropenone with selected reagents are illustrated in equation 67[102]



(67)

VII. OTHER PROPERTIES OF CYCLOPROPENONES

Hückel-type molecular orbital calculations performed in 1959 indicated that cyclopropenone should be resonance stabilized by at least 1.36 β and the diphenyl derivative by 6.16 β[142]. A number of other calculations using various methods (CNDO/2, LCAO-MO-SCF, REPE) also suggest stabilization of the cyclopropenone molecule[143-146]. Various arguments have been made regarding the contribution of the dipolar form **27a**. For example, it has been suggested that the polarity of the carbonyl group in cyclopropenones does not differ greatly from other carbonyl groups if one assumes that the small positive charge normally residing on a carbonyl carbon atom is delocalized over the three-membered ring[147]. Nevertheless, it is to be expected that there would be greater delocalization in cyclopropenone than in the higher homologs, since the electrostatic work required to achieve the dipolar structure should be considerably less[143].

Fortunately, the question of aromaticity has been approached experimentally via thermochemical studies in the case of diphenylcyclopropenone[148]. Careful studies using a rotary-bomb calorimeter as well as a determination of the standard molar enthalpy of sublimation for this compound show that the resonance stabilization in the three-membered ring is 18.6 kcal mol^{-1} if one assumes a ring strain in cyclopropanone of 67 kcal mol^{-1}.

The magnitude of this value supports the view that cyclopropenones are aromatic molecules having significant ground-state stabilization. These thermochemical studies are especially important, since spectroscopic results are rather inconclusive. The ^{1}H-NMR spectra of cyclopropenones[94,95,97] and several monoalkyl derivatives[84,100] exhibit a signal for the ring protons at $\sim \delta 9$, suggesting a significant contribution from the dipolar structure. The ^{13}C spectrum of diphenylcyclopropenone has also been interpreted in terms of a delocalized structure[149]. On the other hand, measurements of the magnetic susceptibility and ^{13}C-NMR spectrum of cyclopropenone itself indicate no appreciable ring current[150], whereas the PE spectrum of cyclopropenone[151] and some of its derivatives[152,153] suggest some cyclopropenium character.

The microwave structure[150] of cyclopropenone has been revised[154] recently. The following bond lengths have been determined: C=C, 1.349 Å; C–C, 1.425 Å; C=O, 1.212 Å. The significant change is the lengthening of the ring double bond from 1.302 to 1.349 Å. This lengthening arises in part from the repulsion between an oxygen lone pair and the bonding cyclopropene orbital and to donation of the lone pair into an antibonding cyclopropene orbital. An X-ray structure of diphenylcyclopropenone as well as the hydrate indicate some cyclopropenium character[155,166].

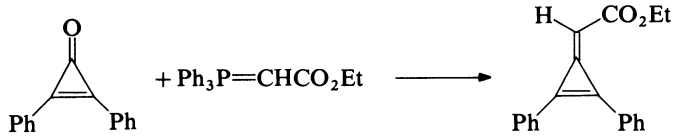
The infrared spectra of cyclopropenones have been assigned using ^{13}C-labeled compounds[156-158]. A strong band at ~ 1850 cm^{-1} arises from coupling of the two double bonds. Another characteristic band at ~ 880 cm^{-1} is a symmetrical stretching interaction of the ring carbon–carbon bonds. It is interesting that no hydrate can be detected by infrared spectroscopy in aqueous solution[94].

VIII. SYNTHESIS OF METHYLENECYCLOPROPENES

Methylenecyclopropene (**74**) and its derivatives are another group of compounds whose stability derives, at least in part, from resonance with the aromatic dipole (**74a**). Stable

(74) (74a)

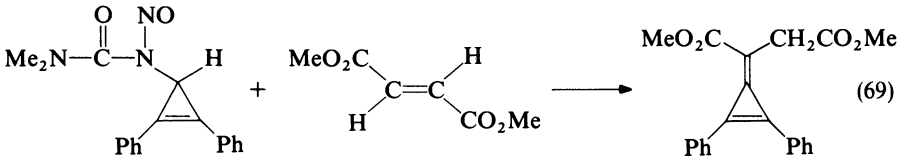
derivatives of methylenecyclopropene were first reported in 1964. Battiste[159] reported the synthesis of **75** via a Wittig reaction on diphenylcyclopropenone (equation 68), whereas



(68)

(75)

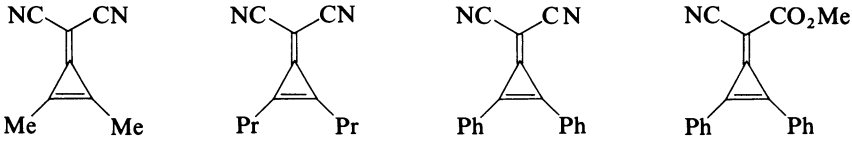
Jones and Denham[160] found that a base-induced reaction of the nitroso compound **76** with dimethyl fumarate yielded **77** (equation 69).



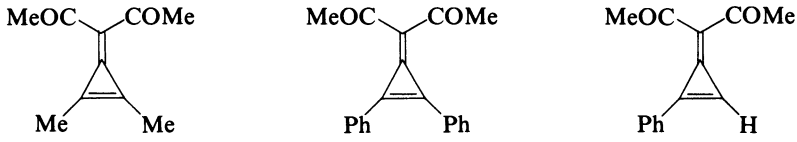
(69)

(76) **(77)**

Both of these methylenecyclopropenes and other examples such as compounds **78–84** reported later (see Table 2) apparently owe much of their stability to the presence of



(78) **(79)** **(80)** **(81)**



(82) **(83)** **(84)**

electron-withdrawing substituents (CN, CO_2R, COR, etc.) which result in delocalization of the negative charge on the substituents attached to the exocyclic carbon.

As expected, many of these compounds are prepared from the cocondensation reactions of cyclopropenones or cyclopropenyl salts. For example, methylenecyclopropene (**75**) can

TABLE 2. Preparation of some methylenecyclopropenes stabilized by electron-withdrawing substituents at the exocyclic carbon

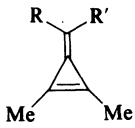
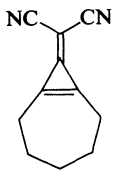
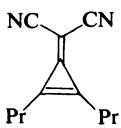
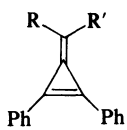
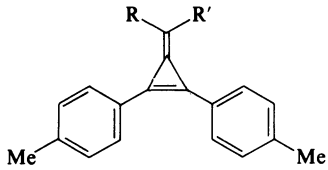
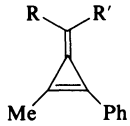
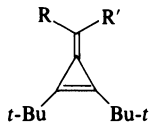
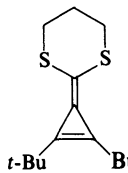
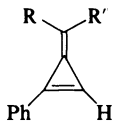
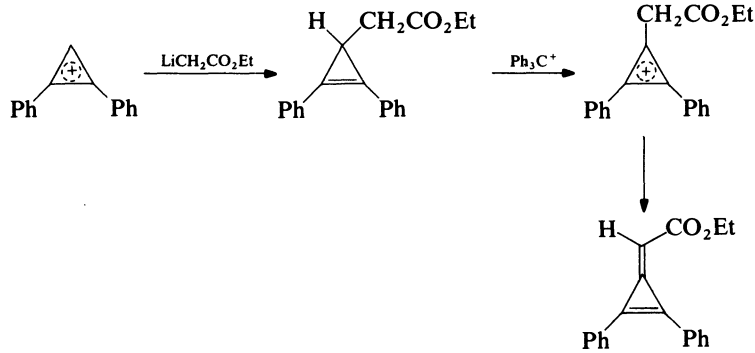
Product	Method[a]	Yield %	Refs.
			
R = R′ = CN	A	41	62
R = CN, R′ = CO_2Me	A	34	62
R = R′ = COMe	B	22	62
R = CN, R′ = COPh	A	35	62
R = CN, R′ = $C_6H_4NO_2$-*p*	A	8	62
R = CN, R′ = NO_2	C	43	62
R, R′ = dimedone	A	58	62
	A	58	62
			
	D	18	163
R = $PhSO_2$, R′ = $(Me)_3Si$	E	70	172
R = *p*-$MeC_6H_4SO_2$, R′ = MeS	E	26	172
R = R′ = CN	A	85	169
	D	24	113
R = CN, R′ = CO_2Me	A	82	169
R = CN, R′ = CO_2Et	A	70	62
	D	15	164
R = CN, R′ = COPh	A	66	214
R = R′ = COMe	B	80	170
R = R′ = COPr	B	80	62
R = COPh, R′ = CO_2Et	B	62	170
R = COMe, R′ = CONHPh	B	78	170
R = COPh, R′ = CHO	B	74	170
R, R′ = dimedone	A	64	172
R, R′ = meldrum acid	A	53	172
R, R′ = indane-1,3-dione	D	64	213
R = H, R′ = $-CPh{=}C(CN)_2$	A	24	62
R = CO_2Et, R′ = $-C(Me){=}C(CN)_2$	A	95	62
R = CN, R′ = NO_2	C	61	62

TABLE 2. *Continued*

Product	Method[a]	Yield %	Refs.
			
R = R′ = CF_3	G	59	174
			
R = R′ = COMe	B	74	77
R = COMe, R′ = CONHPh	B	96	77
R = CN, R′ = NO_2	C	96	62
R = R′ = CN	A	19	62
R, R′ = dimedone	A	65	62
			
R = R′ = CN	A	27	62
			
	E	26	172
			
R = R′ = COMe	B	16	62
R = COMe, R′ = COPh	F	27	62

[a] A, Condensation using diisopropylethylamine; B, metal-chelate; C, ammonium salt of acetic anhydride; D, acetic anhydride condensation; E, Peterson olefination; F, condensation; G, $(CF_3)_2C{=}C{=}O$ plus di-*p*-tolylcyclopropenone.

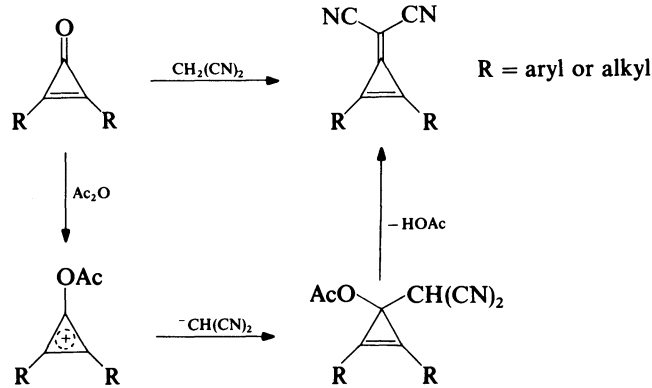
also be prepared by the interesting route illustrated in equation 70[161]. Although this route, as well as the Wittig reaction, has not found wide application in the synthesis of methylenecyclopropenes, it has been used rather extensively in calicene synthesis (see later).



(70)

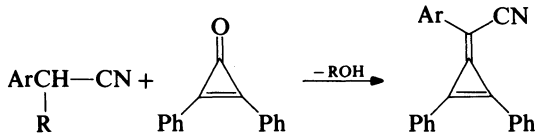
(75)

The condensation of appropriate reactive methylene compounds such as malononitrile with cyclopropenones yields the methylenecyclopropene either directly[162, 163] or via a sequence in which bifunctional acid–base catalysis is employed (equation 71)[113].



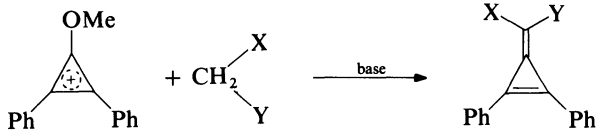
(71)

The reaction of diphenylcyclopropenone with certain aryl malononitriles[165] or aryl cyanoacetones[166] leads to the methylenecyclopropene without the addition of acetic anhydride (equation 72).



(72)

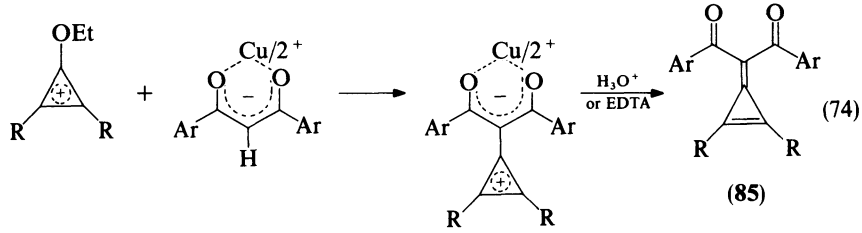
A superior route to these compounds using the condensation procedures involves the use of alkoxycyclopropenyl cations (equation 73)[167]. These can be prepared readily by alkylation of cyclopropenones with trialkyloxonium tetrafluoroborates[76]. This process can be extended to a large number of active methylene compounds if the conditions of the reaction are controlled carefully and the tertiary non-nucleophilic base diisopropylethylamine is used[168, 169]. Otherwise, a large number of side reactions are observed.



(73)

X, Y = CN, CO_2R

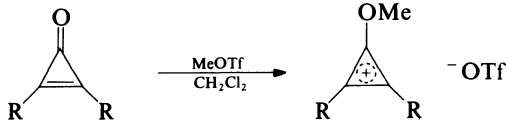
The alkoxy cyclopropenyl cations can also be reacted with copper or zinc chelates of 1,3-dicarbonyl compounds to yield methylenecyclopropenes such as **85**[170] (equation 74).



(74)

(85)

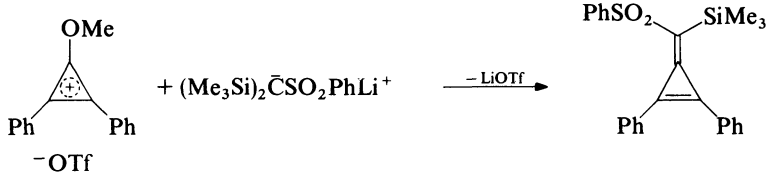
The well-known Peterson olefination reaction has been utilized in the synthesis of several unusually substituted methylenecyclopropenes[171]. The precursor methoxycyclopropenyl triflates can be obtained as stable crystalline salts by addition of methyl triflate to the appropriate cyclopropenone (equation 75). The reaction of these triflates with a variety



(75)

R = Ph, *t*-Bu

of α-silyl substituted anions was shown to yield the methylenecyclopropene[172]. An illustration is provided in equation 76.



(76)

An impressive application of this process is found in the synthesis of methylenecycloproparene derivatives such as **86** (equation 77)[173]. These highly strained

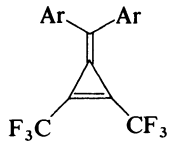
(77)

(86)

R = Ph, Me

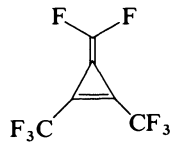
compounds combine into a single molecule the features of methylenecyclopropene as well as *o*-bridged benzenes. Naphthalene derivatives of **86** have also been prepared.

Other methylenecyclopropenes apparently owe their stability to inductive effects brought about by strongly electron-withdrawing groups. Thus 1,2-bis-(trifluoromethyl) 4,4-bis-(*p*-tolyl)methylenecyclopropene (**87**) is a perfectly stable molecule with a dipole

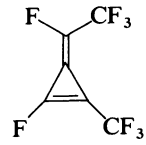


(87)

Ar = *p*-tolyl



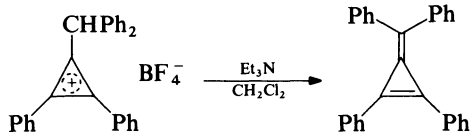
(88)



(89)

moment of 7.42 D[174]. Methylenecyclopropenes **88** and **89** are also stable isolable compounds[175, 176].

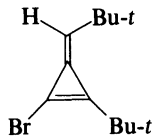
More recently, a number of simple methylenecyclopropenes which are stabilized by either conjugation or by steric protection have been reported. The best example of the former is tetraphenylmethylenecyclopropene (**90**) which is made by the action of base on the cyclopropenyl salt **91** (equation 78)[177]. This air-stable compound can be isolated as



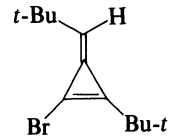
(78)

(91) **(90)**

dark red crystals. Its spectra indicate a considerable contribution from a dipolar structure in the ground state.

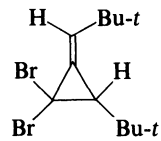


(92)

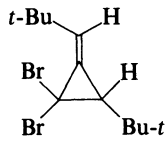


(93)

Sterically protected methylenecyclopropenes **92** and **93** can be prepared by dehydrobromination of **94** and **95**, respectively[178]. Both isomers are thermally labile and

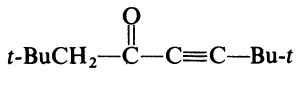


(94)

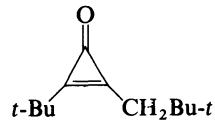


(95)

both react spontaneously with moisture via competing 1,2- and 1,4-addition to yield **96** and **97**, respectively.

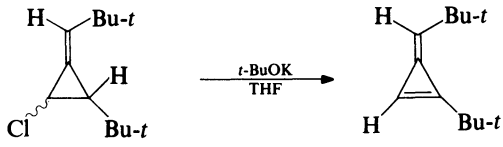


(96)



(97)

The methylenecyclopropene **98** without a bromine substituent has also been prepared by an elimination reaction and shown to be stable up to 0°C (equation 79)[179]. This



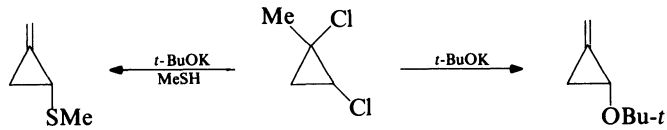
(79)

(98)

approach to the stabilization of C_4H_4 hydrocarbons is well documented and finds elegant application in the synthesis of stable cyclobutadiene and tetrahedrane derivatives[180].

Despite intense theoretical interest, surprisingly few attempts[181–183] to prepare the parent hydrocarbon were reported prior to its synthesis in 1984; however, evidence for simple alkyl methylenecyclopropenes can be found in the base-induced elimination–isomerization reactions of gem-dichlorocyclopropanes[184–186].

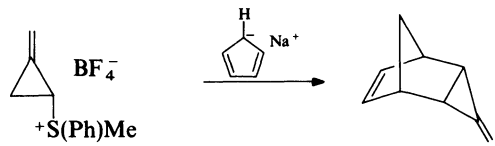
The formation of methylenecyclopropene was surmised from experiments where 1,2-dihalo-1-methylcyclopropanes are treated with base[187, 188]. Thus the reaction of **99** with potassium *t*-butoxide yielded *t*-butoxymethylenecyclopropane **100**. When methanethiol is added to the reaction mixture, **101** is isolated (equation 80). These results can be rationalized in terms of methylenecyclopropene as a reactive intermediate.



(80)

(101) **(99)** **(100)**

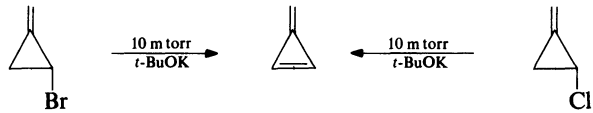
Even more compelling evidence for the intermediacy of methylenecyclopropene is found when (2-methylenecyclopropyl)methylphenylsulfonium tetrafluoroborate (**102**) is treated with sodium cyclopentadienide to yield **103** (equation 81)[189].



(81)

(102) **(103)**

The synthesis of methylenecyclopropene under conditions which allow complete spectral characterization was finally reported in 1984[190, 191]. Dehydrohalogenation of either **104** or **105** in the gas phase at 10 mtorr over potassium *t*-butoxide supported on Chromosorb provided nearly pure methylenecyclopropene (equation 82). The remarkable

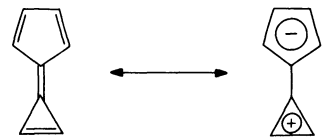


(82)

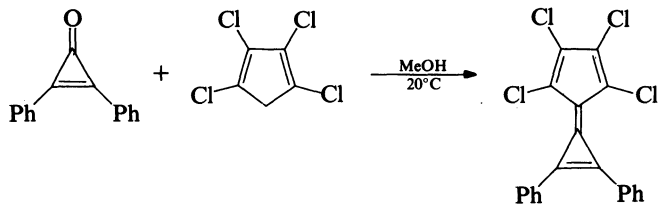
(104) **(74)** **(105)**

stability of methylenecyclopropene (stable below $\sim -75°C$) stands in contrast to cyclobutadiene, an isomer, which appears to dimerize in a diffusion controlled process[192].

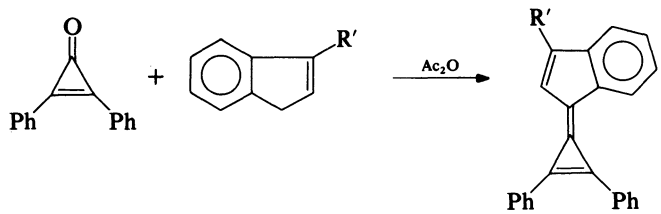
The triapentafulvenes or calicenes[193, 194] constitute another type of methylenecyclopropene which gives some indication of dipolar character and thus a degree of aromaticity. These compounds link the positively charged cyclopropenyl cation to a cyclopentadienyl anion.



They can, in general, be prepared using methods similar to those described above for the methylenecyclopropenes. For example, cyclopropenones can be condensed with cyclopentadienes or indenes under mild conditions[195, 196] to yield the desired product (equation 83 and 84). Similarly, compounds such as the Li, Na, or Grignard reagents of cyclopentadiene,



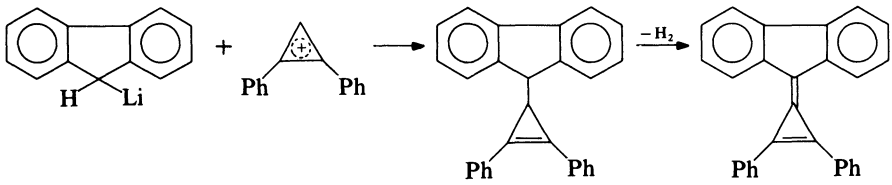
(83)



(84)

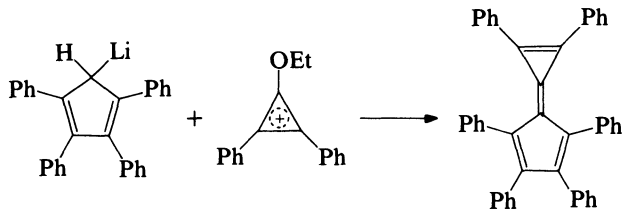
$R' = CN, CO_2R$

indene, or fluorene add to disubstituted cyclopropenyl cations forming the cyclopentadienyl cyclopropenes, which can be transformed to the calicenes (equation 85)[197, 198]. An illustration is provided below[198].



(85)

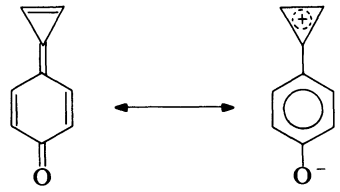
The ethoxy cation **106** was combined with tetraphenylcyclopentadienyl lithium in the synthesis of hexaphenylcalicene[199, 200] (equation 86).



(86)

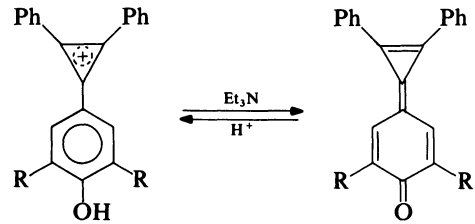
(106)

Quinocyclopropenes have the structural formula **107** and, as such, contribution from dipolar structures must be considered since a benzenoid ring is formed.



(107)

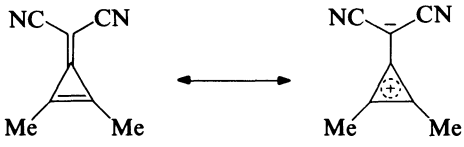
They have been prepared[201, 202] by deprotonation of *p*-hydroxyaryl cyclopropenyl salts (equation 87).



(87)

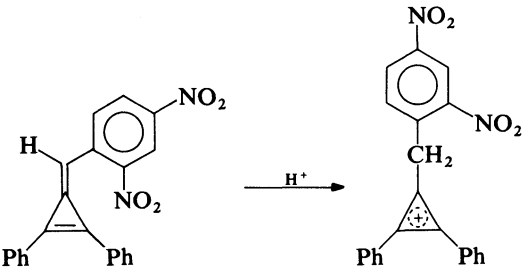
A number of related compounds in which the benzenoid ring is thiophene[203] or a tropone[204, 205] have also been prepared.

The propensity of methylenecyclopropenes to react with electrophiles and nucleophiles is determined by their electronic structure. Thus, methylenecyclopropenes with electron-withdrawing substituents such as **78** fail to protonate in trifluoroacetic acid[113], whereas



(78)

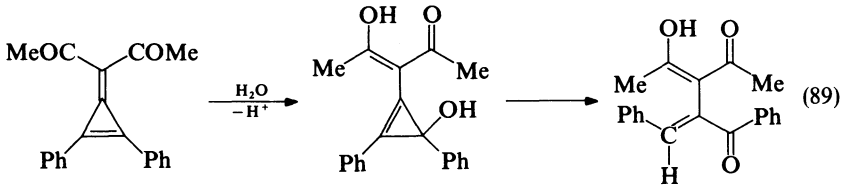
the intensely colored methylenecyclopropene **108** protonates readily in trifluoroacetic acid to yield the colorless cyclopropenyl cation **108a** (equation 88)[62].



(88)

(108) (108a)

Hydration occurs preferentially at the three-membered ring on C(1–2) as illustrated in the reaction of **83** with water[62] (equation 89).



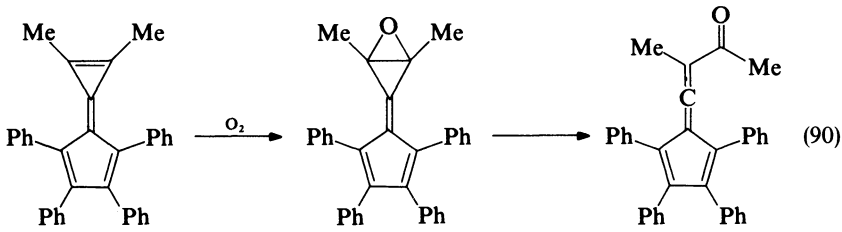
(89)

(83)

The propensity of the parent hydrocarbon towards oxygen and sulfur nucleophiles (RO^-, RS^-) has been noted earlier.

In contrast to the cyclopropenones, the methylenecyclopropenes do not undergo clear thermal transformations. The simpler more reactive members of this family polymerize readily at or near room temperature.

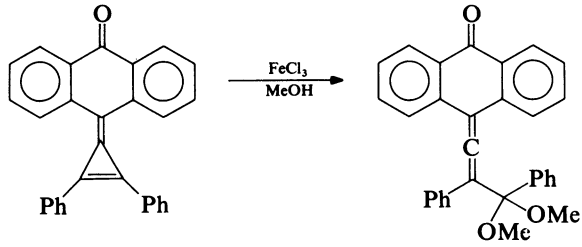
Although the oxidation chemistry of methylenecyclopropenes is not well developed, a



(90)

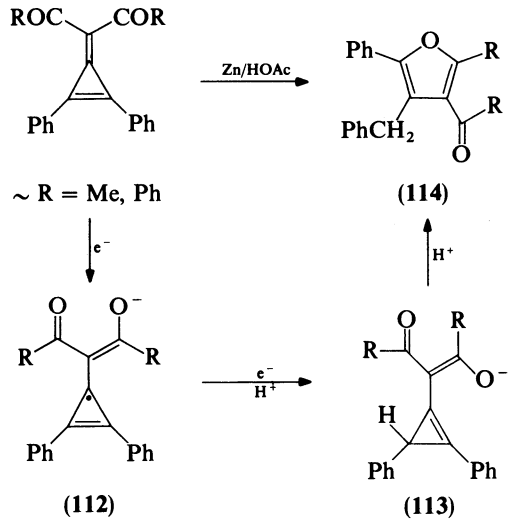
(109) (111) (110)

few studies have been reported. For example, 1,2,3,4-tetraphenyl-5,6-dimethylcalicene (**109**) is oxidized readily on exposure to dioxygen giving **110** probably via intermediate **111** (equation 90)[206]. Cyclopropenylidene anthrones yield similar products upon treatment with ferric chloride in hydroxylic solvents[207] (equation 91).



(91)

A number of very interesting studies have been carried out on the reduction of these compounds. The 4,4-diacyl or dibenzoyl derivative can be reduced to **112** using zinc/acetic acid. The product **114** is thought to result from collapse of the intermediate anion **113** as illustrated in equation 92[62].

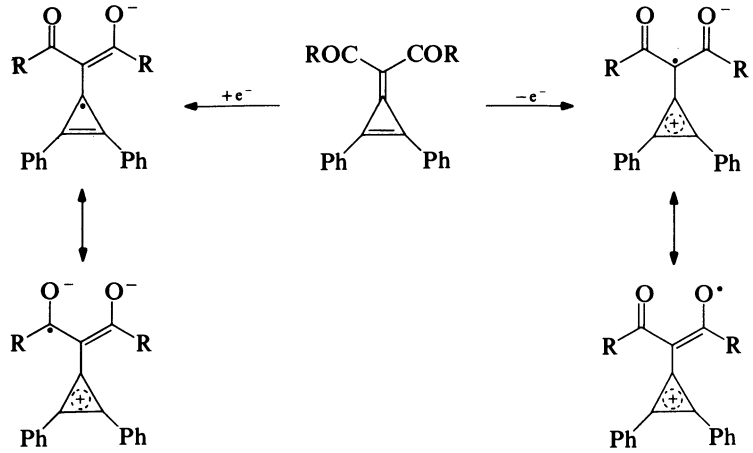


(92)

A polarographic study[62] of the same compound provides evidence for both oxidation and reduction. The reductive process seems to be favored (-1.2 to 1.3 V vs. $+1.6$ to 1.75 V) because of the stabilized enolate-like species (equation 93).

IX. STRUCTURE OF METHYLENECYCLOPROPENE

The structures of several substituted methylenecyclopropenes and calicenes have been determined and reviewed[62]. Of particular interest, however, is structural data of the parent hydrocarbon. The electric dipole moment ($\mu = 1.88$ D) and the heavy atom molecular structure of methylenecyclopropene have been determined by microwave spectroscopy: C=C, 1.323 Å; C–C, 1.441 Å; C=O, 1.212 Å. The experimental and calculated structure



(93)

leads to the conclusion that the dipolar resonance form constitutes about one-fifth of the ground state character, but only contributes a π-delocalization energy comparable to that of 1,3-butadiene[154]. The heat of formation is calculated to be 93.4 kcal mol^{-1}.

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