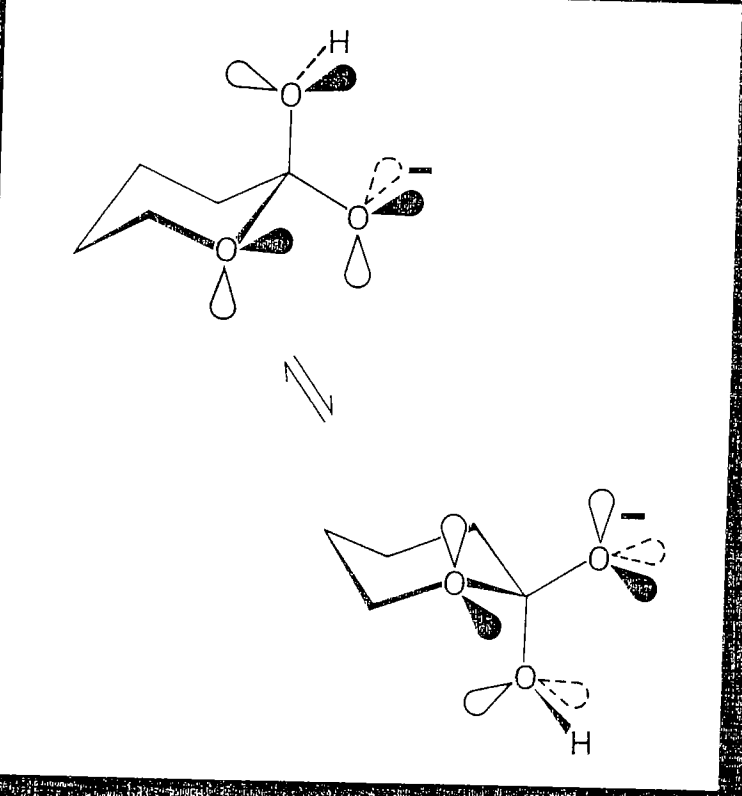
Stereoelectronic Effects in Organic Chemistry

PIERRE DESLONGCHAMPS



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PIERRE DESLONGCHAMPS
Département de Chimie, Université de Sherbrooke, Québec, Canada

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To those who contributed to the development of the concept of stereoelectronic effects

"The first condition to be fulfilled by men of science, applying themselves to the investigation of natural phenomena, is to maintain absolute freedom of mind, based on philosophical doubt. Yet we must not be in the least sceptical; we must believe in science, i.e., in determinism; we must believe in a complete and necessary relation between things, among the phenomena proper to living things as well as in others; but at the same time we must be thoroughly convinced that we know this relation only in a more or less approximate way, and that the theories we hold are far from embodying changeless truths. When we propound a general theory in our sciences we are sure only that, literally speaking, all such theories are false. They are only partial and provisional truths which are necessary to us, as steps on which we rest, so as to go on with investigation; they embody only the present state of our knowledge, and consequently they must change with the growth of science, and all the more often when sciences are less advanced in their evolution."

(from Claude Bernard, 1865)

FOREWORD

The development, during the past thirty years, of the electronic theory of organic chemistry combining the original Robinson theory with the conformational developments of Barton and others, has led to the stereoelectronic theory of organic chemistry. This approach to the understanding of reactivity of organic compounds is used daily by organic chemists, particularly those who have to deal with structurally complex molecules. Unfortunately much of the underlying experimental basis for this general approach is spread widely through the vast literature of the recent period.

In this book Pierre Deslongchamps, an investigator who has made seminal contributions to the stereoelectronic theory, brings together the experimental data and his conclusions derived from them. It is particularly timely that this be done since, by their very nature, stereoelectronic effects are quite subtle and to see the thread of their influences a large body of experimental data is essential. A similar circumstance applied during the formative years of Robinson's theory.

This book will be particularly valuable to all investigators working with complex organic molecules, whether they be synthetic, medicinal or bioorganic chemists, since it will provide a timely view of stereoelectronic effects and how they may be applied, both to rationalise and to predict organic chemical reactivity.

Professor J. E. Baldwin, FRS

University of Oxford
Dyson Perrins Laboratory

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I should like also to thank Professors B. Belleau (McGill), J.M. Cook (Wisconsin-Milwaukee), M.E. Kuehne (Vermont), S.G. Levine (North Carolina), M.W. Makinen (Chicago), and J.D. Wuest (Montreal) who made several suggestions. Particular words of thanks are due to Professors D. Gravel (Montreal), P. Lavallée (Sherbrooke), and Z. Valenta (New Brunswick) who read and corrected the entire draft manuscript.

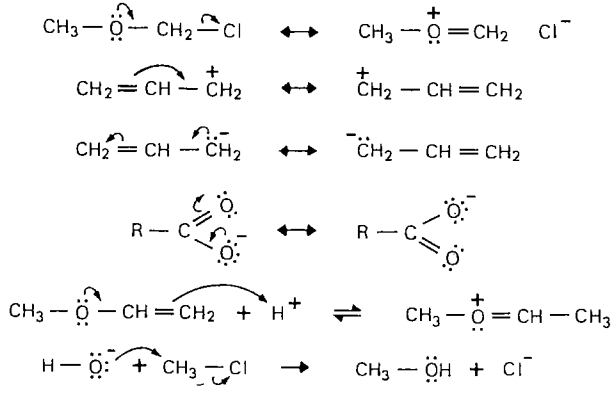
The drawing of the chemical structures, the typing, and the preparation of the camera-ready manuscript was the master-work of Mrs M.-M. Leroux, to whom I wish to express my greatest gratitude.

CONTENTS

CHAPTER 1

INTRODUCTION

The organic chemist made an important step in the understanding of chemical reactivity when he realized the importance of electronic stabilization caused by the delocalization of electron pairs (bonded and non-bonded) in organic molecules. Indeed, this concept led to the development of the resonance theory for conjugated molecules and has provided a rational for the understanding of chemical reactivity (1, 2, 3). The use of "curved arrows" developed 50 years ago is still a very convenient way to express either the electronic delocalization in resonance structures or the electronic "displacement" occurring in a particular reaction mechanism. This is shown by the following examples.



In recent years, experimental evidence has been accumulated which show that this kind of electronic interaction takes place only when the electron pairs are properly oriented in space. Indeed, many results indicate that the reactivity of most types of organic molecules depends upon relative stereochemistry of particular electron pairs, bonded or non-bonded. As a result, the reactivity and the conformational analysis of molecules especially those containing heteroatoms are better understood. It is also through the consideration of the concept of stereoelectronic effects that it becomes possible to acquire the knowledge of the stereochemistry of the transition states of most organic reactions.

This monograph is an attempt to put together all the work which has provided experimental support for the concept of stereoelectronic effects. Reference to theoretical calculation upholding this concept has also been included. The hope of the work is to convince organic chemists that stereoelectronic effects are indeed important and that they should be routinely taken into account when analyzing either the conformation of a particular compound or the course of an organic reaction.

Hydrolysis processes which are key reactions in the biological system are described in the next three Chapters; Chapter 2 covering acetals, Chapter 3 esters, and Chapter 4 amides and related functions. The following three Chapters cover reactions often used by the synthetic organic chemist. Chapter 5 describes reactions which take place at saturated carbon atoms, Chapter 6 deals with reactions on sp_2-type unsaturated systems and Chapter 7 discusses reactions on sp-type unsaturated systems. Chapter 8 is a potpourri of various synthetic organic reactions which could not be appropriately described in the preceding three Chapters. This Chapter describes also how to use stereoelectronic effects to design organic molecules having unusual reactivities and to develop new strategies in organic synthesis. The last Chapter entitled Biological Processes, i.e., Chapter 9, points out the importance of stereoelectronic effects in enzyme-catalyzed reactions and in the understanding of the relationship between chemical structure and biological activity.

It is suggested to read Chapters 2, 3, and 4 first because I believe that the importance of stereoelectronic effects described in the following Chapter will be better appreciated.

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(1) Ingold, C.K. "Structure and Mechanism in Organic Chemistry"; 2nd Ed.; Cornell University Press: Ithaca, N.Y., 1969, Chapter 2.

(2) Robinson, Sir R. "Memoirs of a Minor Prophet"; Elsevier: Amsterdam, 1976, Chapter XI.

(3) Pauling, L. "The Nature of the Chemical Bond"; 3rd Ed.; Cornell University Press: Ithaca, N.Y., 1960.

CHAPTER 2

ACETALS AND RELATED FUNCTIONS

Conformation of acetals

An acetal function can adopt any of the nine gauche conformations described in Fig. 1. Conformers A, B, and D are the mirror images of conformers A', B', and D' respectively. The remaining conformers C, E, and F possess a plane of symmetry. Consequently, the acetal function can in principle exist in the six different conformations A-F. Experimental evidence will be described which shows that the relative stabilities of these various conformers depend on stereoelectronic effects and the standard steric interactions.

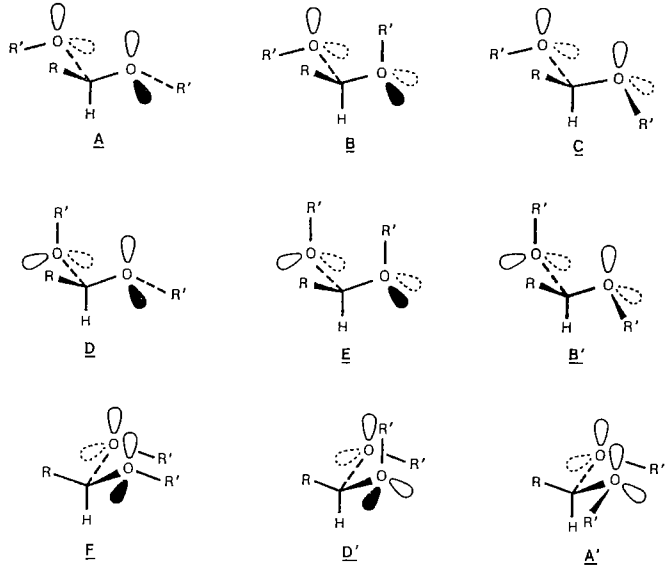


Fig.1

Stereoelectronic effects have long been recognized to influence the configuration and the conformation of acetals, particularly in carbohydrates where these effects were first discovered and discussed in terms of the anomeric and the exo-anomeric effects (1-3). The term anomeric effect introduced by Lemieux in 1958 (4) refers to the tendency of an alkoxy group at C-1 of a pyranose ring to assume the axial rather than the equatorial orientation despite unfavorable steric interactions, whereas the term exo-anomeric effect also introduced by the same author (5) concerns the preferred orientation of the O—R bond of the alkoxy group at the anomeric center.

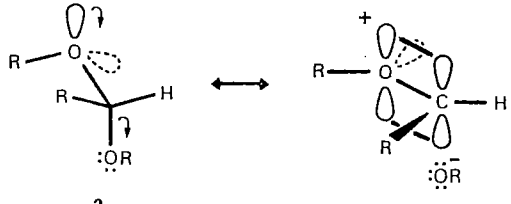
There have been two schools of thought concerning the origin of the anomeric effect (1-3). The first (6-8), considers this electronic effect as destabilizing, due to repulsion by dipole-dipole or electron pair - electron pair (rabbit ear effect) interactions which can be represented by the double headed arrow in structure 1. The second school considers the anomeric effect as a stabilizing electronic effect (9-13) which occurs when an electron pair of an oxygen atom is oriented antiperiplanar to a polar C—X (X= OR, NR_2 or halogen) bond. Stabilization would then be gained by the partial transfer of an electron pair of one heteroatom to another electronegative atom; this electronic transfer being illustrated by the arrows in structure 2.

In practice, it makes little difference whether one believes that the anomeric effect is destabilizing or stabilizing since one can arrive at the same conclusion concerning the relative stability of conformers or isomers. For instance, for a molecule which can take the two conformations 1 and

2, if the anomeric effect is stabilizing, one concludes that 2 is more stable than 1 because 2 has a stabilizing anomeric effect. If one accepts that the anomeric effect is destabilizing, one concludes that 2 is more stable than 1 because 1 has a destabilizing anomeric effect.

It is possible and probably very likely that both types of electronic effects are occurring in the acetal function. In other words, 2 could be more stable than 1 because 2 is stabilized relative to 1 by a partial electron transfer and 1 is destabilized relative to 2 by electronic repulsions. There is presently no experimental technique to differentiate between the two effects. At the present time, many chemists, including myself, prefer to consider the anomeric effect as a stabilizing rather than a destabilizing effect. The main reason is that the concept of stabilization of a system through electronic delocalization is a well established principle in organic chemistry. The resonance theory is indeed based on this principle. I believe that this concept rather than the dipole - dipole or electron pair - electron pair repulsions allows the organic chemist to rationalize his results better.

The anomeric effect in terms of a stabilizing effect can be illustrated by the concept of "double-bond - no-bond resonance" (14, 15) shown by the resonance structures 4 and 3 or by the equivalent modern view (16, 17) that this electronic delocalization is due to the overlap of an electron pair orbital of an oxygen atom with the antibonding orbital of a C—OR sigma bond (12).

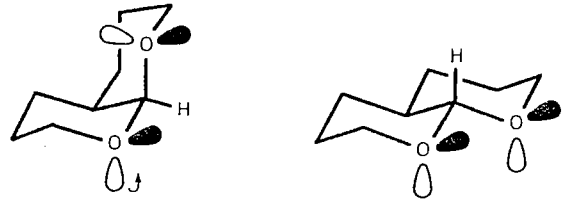


3 4

It has also been suggested (18, 19) that a distinction should be made between the two lone pairs of a given ether-oxygen atom, one being more 2p-like and a better donor than the other lone pair which is more sp^2-like and a poorer donor. As a consequence of this, the 2p-like lone pair of the oxygen atom in a tetrahydropyran ring, for instance, cannot be perfectly antiperiplanar to an axial alkoxy group (12, 20). I prefer to consider that

the non-bonded electron pairs are equivalent and that the ether oxygen is tetrahedral and thus similar to the tertiary amine nitrogen and the tetrasubstituted carbon atom (cf. valence-shell electron pair repulsion theory (21)). However, in the case of the acetal function, when an oxygen atom has one of its electron pairs oriented antiperiplanar to a C—OR bond as in 3, the other resonance structure 4 can be written and the actual situation should correspond to the hybrid of these two resonance structures. The oxygen atom which is donating electrons forms a partial double-bond with the carbon atom, and is therefore partially sp^2 hybridized. Normally, the organic chemist does not write all the resonance structures; he writes one single structure, and applies the resonance theory in his mind. I consider this good practice. I also prefer to use the term "non-bonded electron pair" in place of "lone pair orbital" as it expresses the basis for chemical reactivity (vide infra) in a more precise manner.

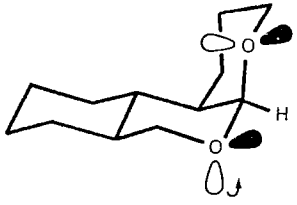
The first precise evaluation of the anomeric effect was realized by Descotes and co-workers in 1968 (22). These authors have studied the acid catalyzed isomerization of the cis and trans bicyclic acetals 5 and 6 and found that, at equilibrium, the mixture contains 57% cis and 43% trans at 80°C. The cis isomer is therefore more stable than the trans by 0.17 kcal/mol. The cis isomer 5 has one (stabilizing) anomeric effect whereas the trans isomer 6 has none. Steric interactions in cis acetal 5 were estimated to be 1.65 kcal/mol (one gauche form of n-butane, 0.85 kcal/mol and an OR group axial to cyclohexane, 0.8 kcal/mol). By subtracting an entropy factor (0.42 kcal/mol at 80°C) caused by the fact that the cis acetal 5 exists as a mixture of two conformations (cis decalin system), they arrived at a value of 1.4 kcal/mol for the anomeric effect.



5 6

More recently, the equilibration of the conformationally rigid cis and trans tricyclic acetals 7 and 8 was carried out (23). The cis acetal 7 is less stable (45% at equilibrium) than the trans acetal 8 by 0.14 kcal/mol. Taking

into account a value of 1.65 kcal/mol for the steric interactions in 7, the anomeric effect becomes 1.5 kcal/mol which confirms the value of Descotes.



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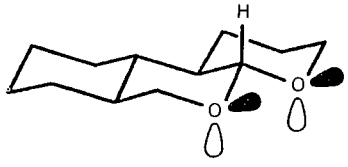
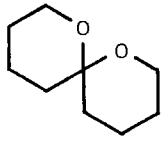


8

The first precise evaluation (24, 25) of both the anomeric and the exo-anomeric effects was obtained by studying 1,7-dioxaspiro[5.5]undecane (9) (Fig. 2). With this system, conformational analysis by low temperature nmr spectroscopy was possible because each conformational change involves a chair inversion which has a relatively high energy barrier. The steric effect could also be easily evaluated, and by adding appropriate alkyl substituents, it was theoretically possible to isolate isomeric compounds which would exist in different conformations.



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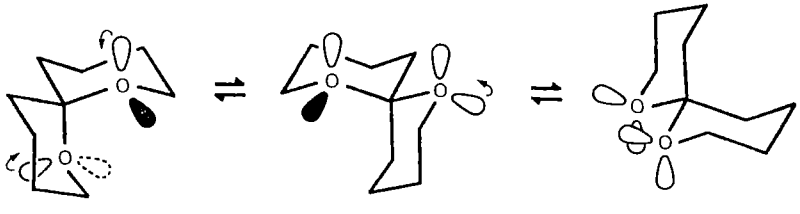


9A 9B 9C

Fig. 2

Compound 9 can exist in the three conformations 9A, 9B, and 9C. Two oxygens in conformer 9A have an electron pair antiperiplanar to a C–O bond, while there is only one such oxygen in conformer 9B and none in conformer 9C. Thus, 9A has two anomeric effects, 9B has one and 9C has none. The assumption was made that, when there are two anomeric effects in the same conformation, they are additive. Accepting the value of Descotes of 1.4 kcal/mol for one anomeric effect, and considering only electronic effects, then 9A and 9B should be more stable than 9C by 2.8 and 1.4 kcal/mol respectively.

The steric effects were then evaluated in the three conformations. In conformer 9A the two oxygens are oriented axially. In conformer 9C, there are two methylene groups oriented axially and in conformer 9B, there is one oxygen and one methylene group axially oriented. When a methylene group is axially oriented it corresponds to two gauche forms of butane evaluated at 0.9 kcal/mol each. When an oxygen is axially oriented, it corresponds to two gauche forms of n-propyl ether ($O-CH_2-CH_2-CH_2$) which were evaluated at 0.4 kcal/mol each. Using these values, the steric effects for conformers 9A, 9B, and 9C are evaluated at 1.6, 2.6, and 3.6 kcal/mol respectively. By taking the stabilizing anomeric and the destabilizing steric effects together, conformer 9A should be more stable than conformers 9B and 9C by 2.4 and 4.8 kcal/mol respectively.* Thus, this analysis led to the prediction that the spiro compound must exist essentially in the conformation 9A only. This prediction was confirmed experimentally by a ^{13}C nmr study at low temperature which clearly showed that compound 9 exists in the conformation 9A only (24, 25).

The methyl substituted spiro system 10 (Fig. 3) was also studied (24, 25). With this system, two isomers 11 and 12 are possible and molecular models show that they can each exist in four different conformations. Evaluation of the anomeric and the steric** effects of each conformation leads to the prediction that isomer 11 exists in the conformation 11A only (0 kcal/mol relative to the other conformations) whereas isomer 12 is a mixture of a major (12A, 2.4 kcal/mol) and a minor (12B, 2.9 kcal/mol) conformer. However, since isomers 11 and 12 are interconvertible (11 can be converted into the mirror image of 12 by opening and reclosure of the acetal function) and

*The relative stabilities are described in terms of relative energy.

**Values of 4.0 and 3.0 kcal/mol were used for the steric interactions of a methyl group 1,3-diaxial to methyl (or methylene) and to oxygen respectively (24).

since 11A is more stable than 12A by 2.4 kcal/mol, only isomer 11 should be formed under thermodynamically controlled conditions, and it should exist in the conformation 11A only. This prediction was completely verified experimentally.

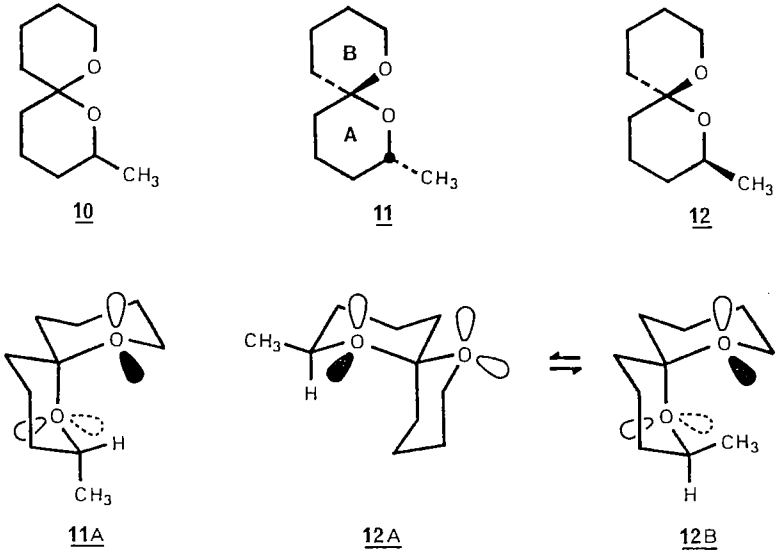


Fig. 3

The spiro compound having two methyl groups was also studied (Fig. 4) (24, 25). With this system there are three possible isomers; two of them (15 and 16) are formed from the cyclization of the dℓ dihydroxyketone 13 whereas the third isomer (17) comes from the cyclization of the isomeric meso dihydroxyketone 14. Under acidic conditions, 15 and 16 should be readily interconvertible and if these acidic conditions are strong enough to allow epimerization of the two dihydroxyketones 13 and 14, the three isomeric compounds 15, 16, and 17 should be interconvertible.

Molecular models show that isomers 15 and 16 can exist in three different conformations each whereas four different conformations are possible for isomer 17. Analysis of the steric and stereoelectronic effects of these different conformations indicated that isomer 15 should exist in only one conformation (15A, 0 kcal/mol), isomer 16 should also exist in only one

conformation (16A, 1.8 kcal/mol) whereas isomer 17 should exist as a mixture of a major (17A, 3.1 kcal/mol) and a minor (17B, 3.7 kcal/mol) conformer.

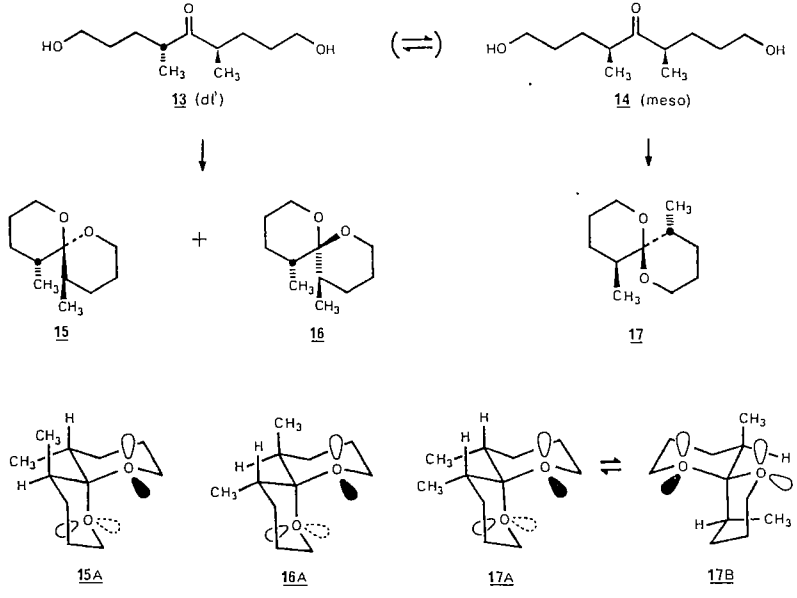


Fig. 4

Cyclization of a mixture of dℓ and meso dihydroxyketones 13 and 14 under mild acid conditions gave a mixture of the three isomeric spiroketals 15, 16, and 17. Low temperature ^{13}C nmr analysis confirmed that isomers 15 and 16 are conformationally rigid and that they exist in the conformations 15A and 16A respectively. Using the same technique, isomer 17 was shown to exist as a mixture of conformers 17A and 17B as predicted. Furthermore, acid equilibration of 15 (or 16) gave a ≈97:3 mixture of isomers 15 and 16, and when isomer 17 was treated under the same conditions it was converted into a 97:3 mixture of 15 and 16. These results are completely consistent with the analysis made above.

With the tricyclic system 18 (Fig. 5), two isomers 20 and 21 are possible from the cyclization of the dihydroxyketone 19, and each can exist in two conformations. It was, however, predicted that each isomer would be conformationally rigid, existing in the conformation 20A (0 kcal/mol) and 21A (2.4 kcal/mol) respectively. Furthermore, since isomers 20 and 21 can be

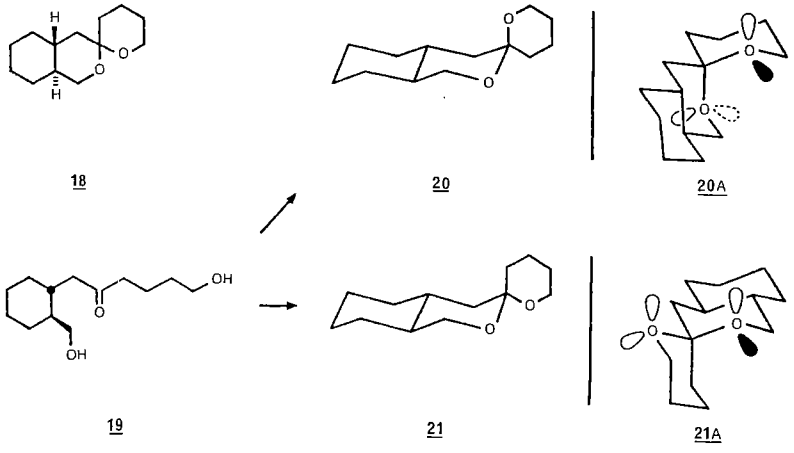


Fig. 5

interconverted by equilibration under acidic conditions, only isomer 20 should be observed experimentally under thermodynamically controlled conditions. Cyclization of dihydroxyketone 19 under very mild acidic conditions gave a mixture of 20 and 21. Compound 20 was shown to exist in the conformation 20A and when 21 was equilibrated under acidic conditions, it was completely converted into the more stable isomer 20 (24, 25).

The tricyclic spiro system having one methyl group was also examined (Fig. 6) (24, 25). This system can give the four isomers 23, 24, 26, and 27. The isomers 23 and 24 come from the cyclization of dihydroxyketone 22 whereas the isomers 26 and 27 come from the cyclization of the isomeric dihydroxyketone 25. In this case, 22 and 25 are not interconvertible under acidic conditions. Each spiro isomer can exist in two different conformations. The theoretical analysis, however, predicted that isomer 23 exists as a mixture of conformers 23A (0.5 kcal/mol) and 23B (0 kcal/mol) whereas isomer 24 exists in the conformation 24A (0 kcal/mol) (Fig. 6). Approximately, a 1:1 mixture of isomers 23 and 24 should therefore be isolated from the cyclization of dihydroxyketone 22.

A similar analysis predicted that isomer 26 should exist in the conformation 26A (0 kcal/mol) whereas isomer 27 should exist as conformer 27A (4.8 kcal/mol). However, since isomers 26 and 27 are interconvertible under acidic conditions, only isomer 26 existing in the conformation 26A should be isolated.

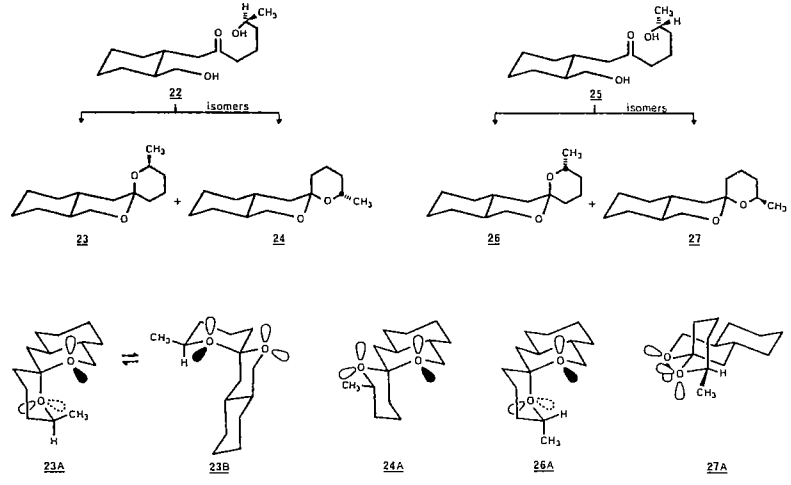


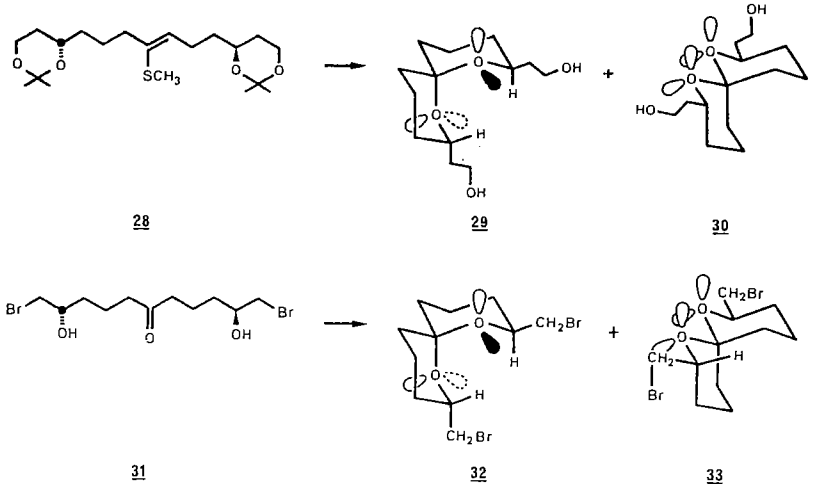
Fig. 6

Cyclization of a mixture of 22 and 25 under acidic conditions gave, as predicted, a mixture of 23, 24, and 26. Furthermore, under acidic conditions, isomer 23 (or 24) was converted into a ≈1:1 mixture of 23 and 24, whereas isomer 26 did not equilibrate under acidic conditions.

The masked tetrahydroxyketone 28 (Fig. 7) which can theoretically give isomers 29 and 30, was found to yield isomer 29 exclusively (26). The structure of 29 was proven by X-ray analysis. Similarly, dibromodihydroxyketone 31 can give either isomer 32 or 33. Upon cyclization, isomer 32 was the product formed (27) and its structure was also established by X-ray (28). The recently reported total synthesis of ionophore A-23187 (29), a polyether antibiotic whih possesses the 1,7-dioxaspiro[5.5]undecane skeleton having a conformation equivalent to 29 and 32 confirms these results.

This series of experiments establishes that 9A (Fig. 2) is the most stable spiroketal conformation; it also demonstrates the importance of two electronic effects in the same function. The value of 1.4 kcal/mol for an anomeric effect must, however, be considered as a minimum value, because similar conclusions would have been reached with a value as high as 1.7 kcal/mol.

Also, the steric interactions might be greater (30) in a substituted tetrahydropyran ring than those of a simple cyclohexane system. For those reasons, the value of 1.4 kcal/mol for an anomeric effect must be considered only as a reasonable minimum value.

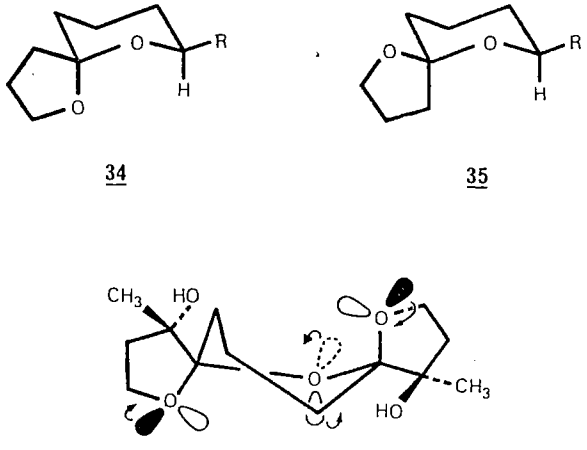


28 29 30

31 32 33

Fig. 7

In the synthesis of the pheromone of the common wasp (31, 32), the diastereoisomer 34 (R=CH_3) was formed preferentially over the isomer 35 which has an oxygen atom in the equatorial orientation. Similar results were also obtained by Kishi and collaborators (33) in the course of the synthesis of monensin, an antibiotic which incorporates the 1,6-dioxaspiro[4.5]decane in its structure. Interestingly, several ionophores possess the 1,6-dioxaspiro[4.5]undecane unit and X-ray analysis (34) revealed that they all exist in a relative configuration equivalent to 34. Descotes and co-workers (35) have prepared several derivatives of 1,6-dioxaspiro[4.5]decane and have shown that 34 (R=H) with the oxygen in the axial orientation is the preferred arrangement. They further report that compound 36 exists in the conformation shown. Interestingly, each ether oxygen in 36 has an electron pair antiperiplanar to a polar C—O bond. This is certainly a direct manifestation of the stereoelectronic effects which cause the tetrahydropyran ring to exist in a twist-boat conformation.



34 35

36

The six conformations A-F of 1,1-dimethoxyethane (R=R'=CH_3 in Fig. 1) can now be analyzed. Conformers D, E, and F have two anomeric effects, A and B have one and C has none. E and F can be eliminated on the basis of the rather strong steric interactions, and by taking a value of 0.9 kcal/mol for the gauche form of butane and 0.4 for that of n-propyl ether ($CH_2CH_2CH_2O$), the relative stabilities of the remaining conformers become D (0 kcal/mol) > A (1.0) > B (1.9) > C (2.9).

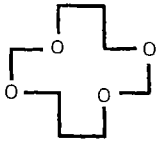
Thus, 1,1-dimethoxyethane should exist as a mixture of a major (D) and two minor conformers (A and B). It is also conceivable that the anomeric effect for the oxygen of an alkoxy group is larger than that of a tetrahydropyran ring because the oxygen atom of an alkoxy group should more easily become trigonal permitting a larger electronic delocalization (36). In that case, the population of conformer D would be even greater. In fact, dipole moment studies revealed that dialkoxyacetals exist in the preferred conformation D (37).

The most simple acetal, i.e. dimethoxymethane, can adopt only four conformations which correspond to those of A, C, D, and E in Fig. 1 (R=H). Conformer E can be readily eliminated and the relative stabilities of the others can be evaluated to be D (0 kcal/mol) > A (1.5) > C (2.5). Thus, in dimethoxy-

methane the preferred conformation is D. In accord with this conclusion, electron diffraction studies of the gas show that D is strongly dominant (38). The same conformation was also found in polyoxymethylene by X-ray analysis (39). The cyclic unstrained oligomers of formaldehyde are also known to adopt this confirmation (40).

As we have seen, the anomeric effect confers a double-bond character to each C−O bond of conformer D; the energy barrier for a C−O bond rotation in acetals must therefore be higher than that observed in simple alkanes. Borgen and Dale (41) may have provided the first evidence for this point by observing that 1,3,7,9-tetraoxacyclododecane (37) has a much higher conformational barrier (11 kcal/mol) than comparable 12-membered rings such as cyclododecane (7.3 kcal/mol (42) or 1,4,7,10-tetraoxacyclododecane (5.5 and 6.8 kcal/mol (43)). It was also shown that the two 1,3-dioxa groupings in 37 exist in a conformation identical to that of dimethoxymethane, i.e. the conformation D.

Anet and Yavari (44) have studied chloromethyl methyl ether by low temperature proton nmr spectroscopy. Their results show that this compound exists in the gauche conformation 38 and they observed a barrier of 4.2 kcal/mol for the rotation of the $O-CH_2Cl$ bond. This barrier is appreciably higher than that expected on the basis of steric repulsion alone. A rough estimate of the steric barrier is 2 kcal/mol, and they concluded that the anomeric effect increases the barrier to rotation of the $O-CH_2Cl$ bond by approximately 2 kcal/mol.



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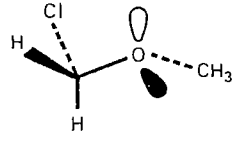
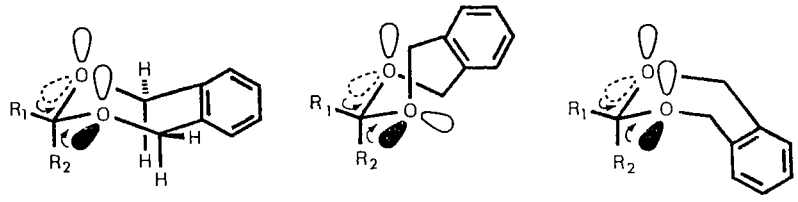
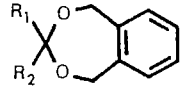


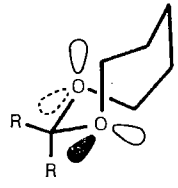
38

Recent results by St-Jacques and collaborators (45) have revealed that the ring conformation in 2,4-benzodioxepin which can be the chair 39 (Fig. 8), the twist boat 40 or the boat form 41, was determined by the nature of substitution. A chair (39) with a minor amount of the twist-boat (40) was observed for the non substituted compound 42, whereas the chair form was found for the methyl derivative 43 and the twist boat-form for the dialkyl derivatives 44, 45, and 46.



39 40 41





47

42 $R_1 = H$, $R_2 = H$
43 $R_1 = CH_3$, $R_2 = H$
44 $R_1 = CH_3$, $R_2 = CH_3$
45 R_1, $R_2 = CH_2-(CH_2)_2-CH_2$
46 R_1, $R_2 = CH_2-(CH_2)_3-CH_2$

Fig. 8

Interestingly, the chair 39 and the twist-boat 40 each have two anomeric effects. The energy difference between the two forms in the simple 2,4-benzodioxepin 42 could be explained by a greater steric interaction in the chair form between the axial hydrogens on C_2, C_4, and C_7. In compound 43, it appears that the chair form 39 ($R_1 = CH_3$) with an equatorial methyl is preferred over the twist-boat 40 ($R_1 = CH_3$) with an isoclinal methyl group because in the latter case, the methyl group has a significant non-bonded repulsive interaction with the methylene group gauche to it. Finally, steric interactions should largely favor the twist-boat 40 over the chair 39 in the disubstituted derivatives 44-46. In these compounds, there is a severe steric repulsion between the axial alkyl group (R_2) and the hydrogens at C_4 and C_7 when they exist in the chair form 39. Part of this steric interaction is not present in the twist-boat 40.

Anet and collaborators (46) as well as Dale and co-workers (47) have also shown the 8-membered ring, 1,3-dioxacyclooctane and some derivatives, to exist only in the boat conformation 47. Conformer 47 has two anomeric effects and is virtually the same as that found in 40 or in dimethoxymethane.

On the basis of the above results and discussion, the glycosides can now be considered. Efforts have been made previously to evaluate the magnitude of the anomeric effect by undertaking equilibration studies between equatorial and axial isomers at the anomeric center in carbohydrates (48), in monosubstituted 2-alkoxytetrahydropyrans (49, 50) and in more rigid systems (51). The anomeric effect has been evaluated to be of the order of 1.2 to 1.8 kcal/mol from these studies. In these evaluations, the conformation of the OR group in the axial and in the equatorial isomer was not considered; the influence of the exo-anomeric effect was therefore neglected (3). Nevertheless, these studies demonstrated the importance of the anomeric effect.

α and β-Glycosides can adopt conformations $\underline{A}_1$, $\underline{A}_2$, $\underline{A}_3$ and $\underline{E}_1$, $\underline{E}_2$, $\underline{E}_3$ respectively (Fig. 9). The relative proportions of these various conformers should be influenced by the usual steric interactions and by stereoelectronic effects. Conformer $\underline{A}_3$ can be immediately eliminated for steric reasons. Conformer $\underline{A}_1$ has two anomeric effects, conformers $\underline{A}_2$, $\underline{E}_1$, and $\underline{E}_2$ have one each whereas conformer $\underline{E}_3$ has none. Taking into account the usual steric effects and the anomeric effect, this analysis predicts that the relative stability is $\underline{A}_1$ (0 kcal/mol), $\underline{A}_2$ (1.9), $\underline{E}_1$ (0.6), $\underline{E}_2$ (1.5), and $\underline{E}_3$ (2.5). On that basis, the α-isomer exists essentially as conformer $\underline{A}_1$ whereas the β-isomer

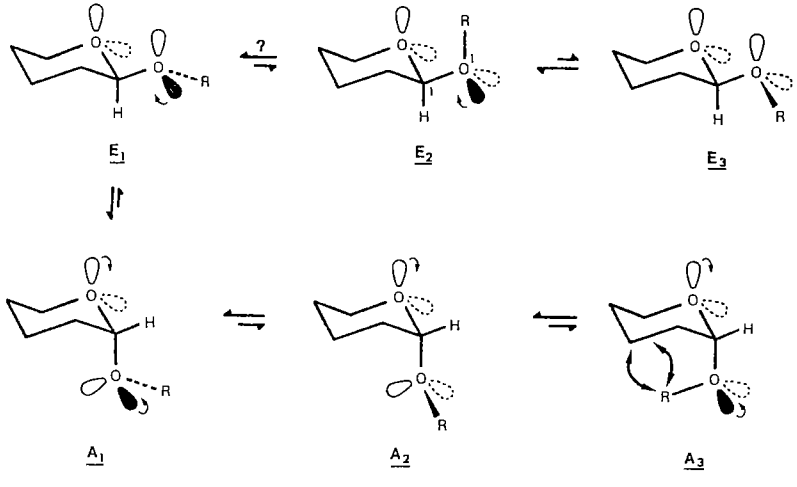


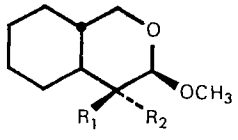
Fig. 9

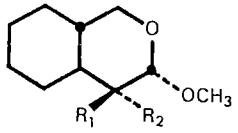
would be a mixture of $\underline{E}_1$ and $\underline{E}_2$ where $\underline{E}_1$ largely predominates. Also, in a conformationally rigid system, the α-isomer should be formed preferentially under equilibrating conditions, in agreement with experimental results; Eliel and Giza (50) found a difference in stability valued at 0.7-0.8 kcal/mol in favor of the axial over the equatorial isomer of 1-methoxy-5-methyltetrahydropyran.

Acid equilibration of the equatorial and axial bicyclic acetals 48 and 49 (Fig. 10) has been carried out (52) and the result was compared with those of the monomethyl acetals 50 and 51, and the gem-dimethyl acetals 52 and 53. Each pair of isomers gave essentially an identical result, i.e. 33% of the equatorial and 77% of the axial isomer (±2%) after equilibration in benzene at 70°C. This corresponds to a ΔG of ≈0.8 kcal/mol, a value close to that predicted for the relative stability of rotamer $\underline{A}_1$ over $\underline{E}_1$ (0.6 kcal/mol).

Based on steric effects only, the equatorial bicyclic acetal 48 can take the three conformations 54, 55, and 56 whereas the axial isomer 49 can exist in the conformations 57 and 58. The equatorial monosubstituted acetal 50 can take only the conformations 54 and 55 whereas the axial isomer 51 must exist exclusively in the conformation 57. Finally, the equatorial and axial gem-dimethyl acetals 52 and 53 are essentially locked in conformations 54 and 57 respectively. Note that 54, 55, and 56 correspond to conformers $\underline{E}_1$, $\underline{E}_2$, and $\underline{E}_3$ whereas 57 and 58 correspond to conformers $\underline{A}_1$ and $\underline{A}_2$ respectively. The equilibration of each pair of axial and equatorial isomers gave a similar result. Since the isomers 52 and 53 exist only in conformations $\underline{E}_1$ (54) and $\underline{A}_1$ (57) respectively, it can be concluded that the population of conformers $\underline{E}_2$ (55), $\underline{E}_3$ (56), and $\underline{A}_2$ (58) must be negligible in the case of the other acetals (49-52). It is known that the anomeric effect becomes less important in polar solvents (49, 50, 53). This phenomenon was observed when the equilibration was carried out in methanol, as the relative percentage of the axial isomer became less important (66% of 49 and 51 and 62% of 53).

The relative proportion of conformers can be established by nmr spectroscopy provided that the various conformers have sufficiently different coupling constants. This method has, however, the disadvantage that small percentages of some conformers will be difficult to detect. Using this method, Lemieux and co-workers (36) were unable to detect the presence of conformers $\underline{E}_2$, $\underline{E}_3$, and $\underline{A}_2$ in β and α-glycosides. Furthermore, no other experimental methods

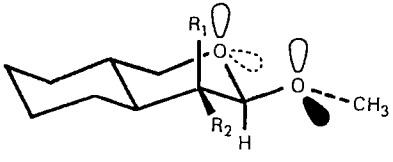




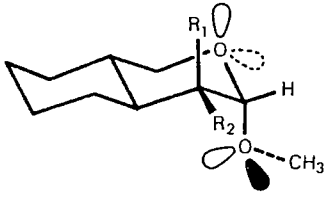
48 $R_1 = R_2 = H$ **49**

50 $R_1 = H,\ R_2 = CH_3$ **51**

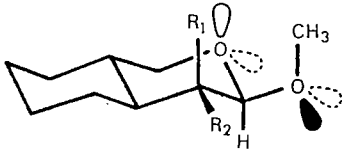
52 $R_1 = R_2 = CH_3$ **53**



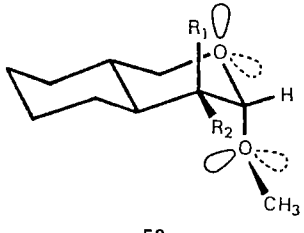
54



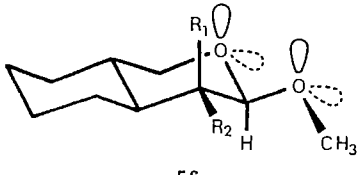
57



55



58



56

Fig. 10

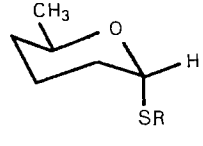
including X-ray (54) and dipole moment studies (53, 55, 56) indicate that α and β-glycosides exist in conformations other than $\underline{A}_1$ and $\underline{E}_1$ respectively.

It is rather surprising that conformer $\underline{E}_2$ cannot compete with conformer $\underline{E}_1$ because they differ by only one gauche form of butane (0.9 kcal/mol). The experimental results suggest that $\underline{E}_1$ and $\underline{E}_2$ should be separated by over 2 kcal/mol. It was suggested (36) that this unexpected situation could be mainly the result of a short $C_1 - O_1$ bond which would amplify the steric interaction in $\underline{E}_2$, because the anomeric effect of an alkoxy oxygen (exo-anomeric effect) would be larger than that of a tetrahydropyran oxygen (cf. p. 15). By comparing bond lengths (X-ray) in glycosides, Lemieux has suggested that the exo-anomeric effect could in fact be stronger. However, there still remains the possibility that a small percentage of $\underline{E}_2$ exists in equilibrium with $\underline{E}_1$, but the experimental technique to observe it has yet to be found (57).

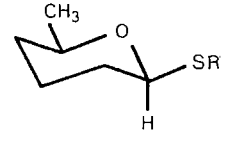
Conformation of mono and dithioacetals

Stereoelectronic effects should also be observed when one or both oxygens of the acetal function are replaced by another heteroatom such as a sulfur or a nitrogen atom. Compounds having sulfur atoms will first be considered.

Eliel and Giza (50) have studied the acid equilibration of the isomeric 2-alkylthio 6-methyltetrahydropyrans **59** and **60** ($R = CH_3$ and $(CH_3)_3C$). They found about 65% of axial isomer **59** indicating that the monothioacetal function possesses an anomeric effect although it is weaker than that of the acetal function. Zefirov and Skekhtman (58) have arrived at a similar conclusion by studying 2-phenylthio and 2-ethylthiotetrahydropyran.



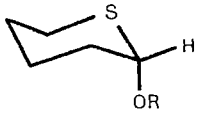
59



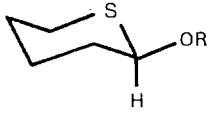
60

2-Alkoxythiatetrahydropyrans were also studied (58, 59). It was found that the major isomer (90%) had the axial conformation **61** rather than the equatorial conformation **62** when R is a methyl or a propyl group. Also, Perlin and Nam Shin (60) have carried out the methanolysis of 5-thio-D-galactose

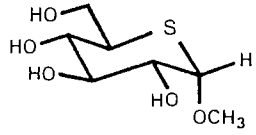
which yielded the α-glycoside 63 almost exclusively. These results suggest that the anomeric effect is appreciable in these compounds. Alkylthiothiapyrans (61 and 62, OR=SR) were also investigated and were shown to exhibit an anomeric effect (61).



61



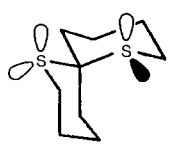
62



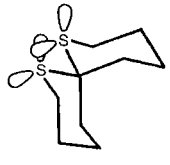
63

1,7-Dithiaspiro[5.5]undecane can exist in the three conformations 64A, 64B, and 64C (Fig. 11). Conformer 64A which has the two sulfurs axially oriented can have two anomeric effects, conformer 64C which has the two sulfurs equatorially oriented has no anomeric effects and conformer 64B with one sulfur axially oriented has only one anomeric effect. Taking into account the steric effects (0.9 kcal/mol for a gauche form of butane and 0.4 kcal/mol for a gauche form of $S-CH_2-X-CH_2$) and an anomeric effect of 1.4 kcal/mol, the relative stabilities 64A, 64B, and 64C are 0, 2.4, and 4.8 kcal/mol. On that basis, this compound must be essentially conformationally rigid existing in the conformation 64A only. This prediction was verified experimentally (25, 62), and further confirmation was found by the study of the acid catalyzed cyclization of ketone dithiol 65. This compound can give either isomer 66 or 67 which can take two different conformations each.

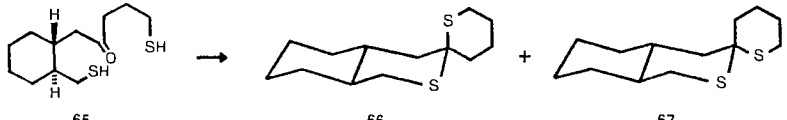
64A



64B



64C

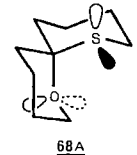


65 66 67

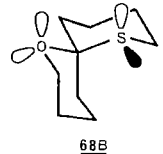
Fig. 11

The detailed analysis of these conformers showed that 66 exists in a conformation equivalent to 64A only. Similarly, 67 would also exist in a conformation equivalent to 64B only. This analysis further predicted that 66 is more stable than 67 by 2.4 kcal/mol and since these isomers can be interconverted by equilibration under acidic conditions, isomer 66 should be the major isomer formed under thermodynamically controlled conditions. Cyclization of 65 under equilibrating conditions gave 66 and 67 in a 98:2 ratio and 66 was shown to exist in a conformation equivalent to 64A. The fact that a small percentage of 67 was detected at room temperature shows that, at sufficiently low temperature, less than 0.1% of 67 would be present. This result confirms that, at low temperature, 1,7-dithiaspiro[5.5]-undecane exists essentially in the conformation 64A only. The anomeric effect for a sulfur atom in the dithioacetal function must therefore be of the order of 1.4 kcal/mol.

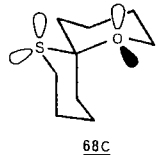
Molecular models show that 1-oxa-7-thiaspiro[5.5]undecane can take four different conformations 68A-D (Fig. 12) where 68A has two anomeric effects, 68B and 68C one and 68D none. Accepting again a value of 1.4 kcal/mol of stabilization for each anomeric effect, and after taking the steric effects into consideration, the relative stabilities were predicted to be 0, 2.4, 2.4, and 4.8 kcal/mol for 68A-D respectively. Thus, on that basis, 1-oxa-7-thiaspiro[5.5]undecane must be essentially conformationally rigid existing as 68A only. Again, the experimental results were in complete agreement (25, 62).



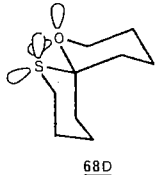
68A



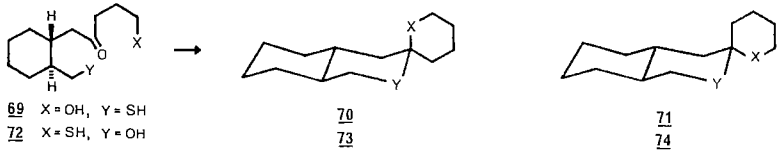
68B



68C



68D



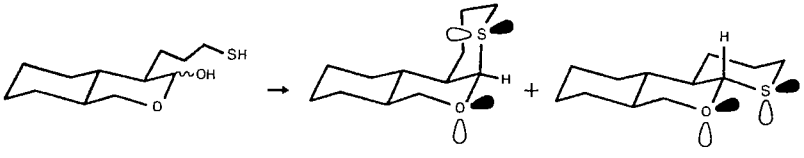
69 X = OH, Y = SH
72 X = SH, Y = OH

70 73 71 74

Fig. 12

This analysis was confirmed by the cyclization studies of hydroxyketone thiols 69 and 72. Compound 69 gave on cyclization the isomer 70 rather than the isomer 71 which has an equatorial oxygen. Similarly, cyclization of 72 gave 73 only; the isomer 74 was not observed. It was further shown that compounds 70 and 73 exist in a conformation equivalent to 68A, which has two anomeric effects.

The hemiacetal thiol 75 (Fig. 13) gave on acid cyclization an equilibrium mixture of cis and trans monothioacetals 76 and 77 in a 1:1 ratio (63). If a value of 1.7 kcal/mol is accepted for the steric effects in 76 (two gauche forms of SCH_2XCH_2 = 0.8 kcal/mol and one gauche form of butane = 0.9 kcal/mol), the anomeric effect for the ether oxygen in 76 must also be equal to 1.7.

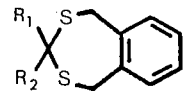


75 76 77

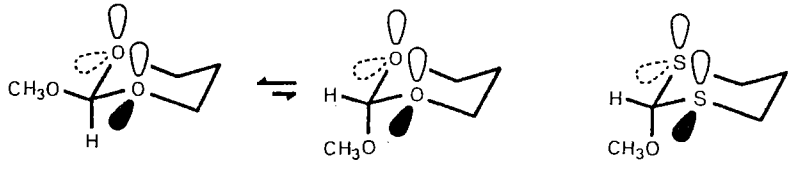
Fig. 13

Sauriol-Lord and St-Jacques (64) have studied 2,4-benzodithiepin 78 and the substituted derivatives 79-82 (Fig. 14). They found that these compounds exist in the chair form 39 (O=S) (Fig. 8), except for the derivative 82 where 13% of the twist-boat 40 (O=S) was detected. The fact that essentially only the chair form was observed in these compounds would simply be due to the long C – S bonds which attenuate the effects of steric repulsions in conformer 39 (O=S). This is in accord with the fact that in contrast to 2-methoxy-1,3-dioxane which exists as a 7:3 mixture of equatorial conformer 83 and axial conformer 84, 2-methoxy-1,3-dithiane has been found to exist solely in the axial form 85.

The same authors have also studied compounds 86 and 87 having a methoxy group (Fig. 15). These compounds could exist either in the chair form with an axial (88) or an equatorial methoxy group (89), or in the twist-boat 90. Conformer 88 is disfavored sterically but is favored electronically, whereas the twist boat 90 with a syn clinal methoxy group is favored electronically and does not suffer from severe steric hindrance. It was found

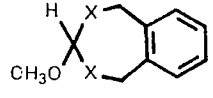


78 R_1 = H, R_2 = H
79 R_1 = CH_3, R_2 = H
80 R_1 = CH_3, R_2 = CH_3
81 R_1, R_2 = $CH_2-(CH_2)_2-CH_2$
82 R_1, R_2 = $CH_2-(CH_2)_3-CH_2$

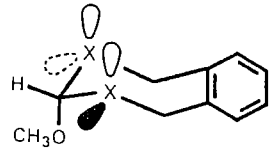


83 84 85

Fig. 14



86 X = O
87 X = S



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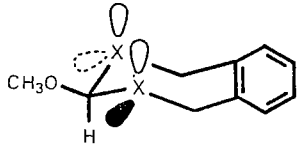

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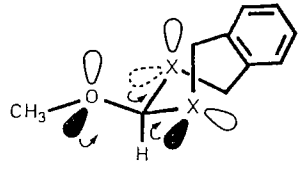


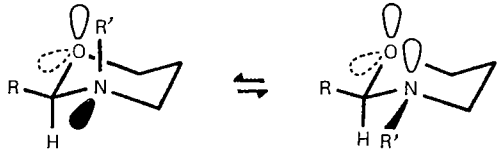
90

Fig. 15

that contrary to compound 43 which exists in the chair form 88 (X=O and OCH_3=CH_3), compound 86 exists in the twist-boat 90 (X=O) which has maximum electronic delocalization and minimum steric effects. Compound 87 was however found to exist as the chair 88 (X=S) and this is explained by electronic delocalization due to an axial methoxy group and less important steric repulsion because of the long C−S bond.

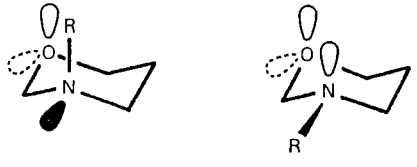
Conformation of 1,3-oxazines and 1,3-diazines

The preceding results demonstrate conclusively that the anomeric effect is important in the case of mono and dithioacetals. The following discussion will show that this effect is equally important in the case of an acetal function having one or two nitrogen atoms.



91 92

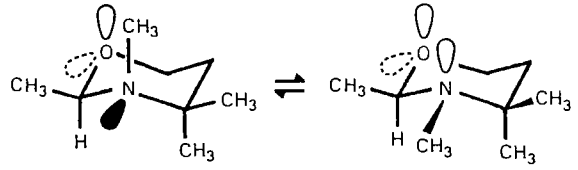
NMR studies at low temperature strongly suggest that, in tetrahydro-1,3-oxazine, conformer 91 (R=R'=H) makes the major contribution to the equilibrium 91 ⇌ 92 (65). The same conclusion was reached for the case where R=CH_3 and R'=H. Two anomeric effects are possible in conformer 91 and only one in conformer 92; the greater stability of 91 can therefore be rationalized by the extra anomeric effect of the nitrogen atom.



93 94

N-substituted tetrahydro-1,3-oxazines were also studied. It has been suggested (66) that conformer 93 with the N-alkyl group in the axial orientation, is more stable than 94 when R is either a methyl or a benzyl group. It was also found that the contribution made by conformer 95 is appreciable and it may dominate conformer 96 in tetrahydro-3,4,4,6-tetramethyl-1,3-oxazine.

Furthermore, Riddell and Lehn (67) have been able to show that when R' is a methyl group and R is either a hydrogen atom or a p-nitro benzyl group, conformers 91 and 92 exist in approximately equal proportion.

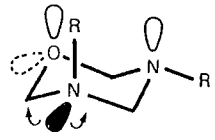


95 96

This last study is quite interesting because it permits an evaluation of the anomeric effect for the nitrogen atom. Conformer 91 with the axial N-methyl group should be less stable than conformer 92 by approximately 1.3 kcal/mol on the basis of steric effects (one gauche form of n-butane, ≈0.9 kcal/mol and one gauche form of CH_3-N-CH_2-O, ≈0.4 kcal/mol). The second anomeric effect caused by the equatorial orientation of the nitrogen electron pair in 91 must compensate for the steric effect. An approximate value of 1.3 kcal/mol must therefore be taken for that electronic effect, a value close to that estimated for the oxygen atom of the acetal function.

97 98

Recently, Crabb, Turner, and Newton (68) have observed that perhydropyrido-[1.3]oxazine exists as a ≈9:1 mixture of the trans and the cis forms 97 and 98. The cis form 98 has two anomeric effects (-2.8 kcal/mol), two gauche forms of butane (1.8 kcal/mol) and one gauche form of n-propyl ether (0.4 kcal/mol) whereas the trans form 97 has only one anomeric effect (-1.4 kcal/mol). On that basis, the trans form 97 should be more stable than the cis form 98 by about 0.8 kcal/mol, in agreement with the experimental result. Katritzky and co-workers (69) have also shown that 1-oxa-3,5-diaza and 1,3-dioxa-5-aza cyclohexane derivatives exist respectively in the conformations 99 and 100. With an alkyl group in the axial orientation, both conformations gain two anomeric effects.



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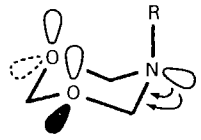
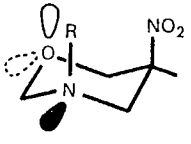


100

Interestingly, Allingham et al. (66) have analyzed a series of N-alkyl 5-nitrotetrahydro 1,3-oxazines and concluded that there is a preference for the N-alkyl axial conformer 101 when the alkyl substituent is methyl, ethyl or propyl and a preference for the N-alkyl equatorial conformer 102 when the substituent is isopropyl, cyclohexyl or t-butyl. Thus, 101 is still preferred despite the 1,3-diaxial steric interaction between the nitro group and a primary N-alkyl group. Finally, Katritzky et al. (70) have proposed the conformation 103 as the major one for compounds 104 and 105.



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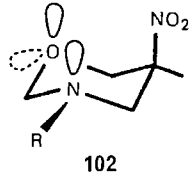

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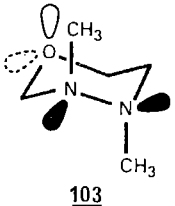

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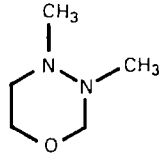

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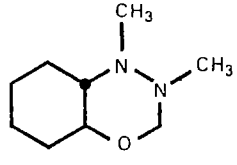
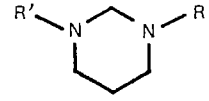


105

Several groups (65, 71-75) have studied the 1,3-diazane system 106 (R=R'=H and/or CH_3) and found that these compounds exist as a mixture of conformers 107 and 108. In these studies, the conformation 109 with two anomeric effects was not considered. It is conceivable that when R=R'=H, the most stable conformation is 109 rather than 108. Also, when R=CH_3 and R'=H, conformer 109 with its second anomeric effect to compensate for the steric effect caused by the axial N-methyl group could compete with conformer 108 which

has only one anomeric effect. These predictions have not yet been verified experimentally.



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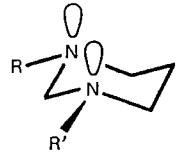

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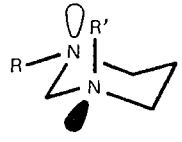

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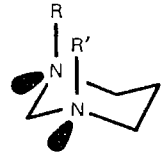


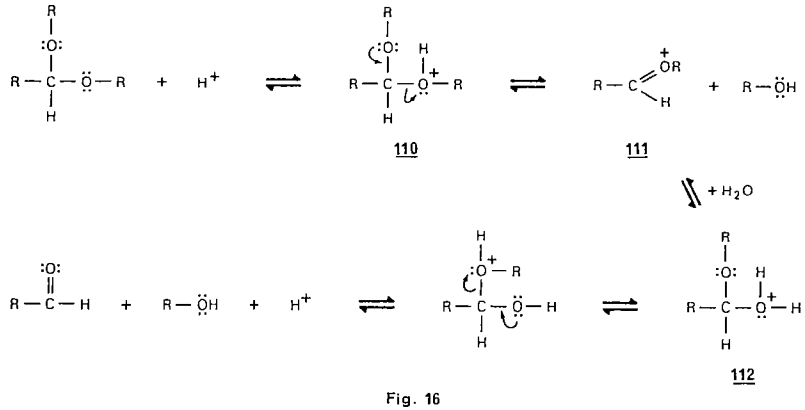
109

Formation and hydrolysis of the acetal function

We have presented experimental results which demonstrate the influence of stereoelectronic effects on the configuration and the conformation of the acetal function. A pertinent question which follows is whether or not these stereoelectronic effects play a similar role in the formation and in the hydrolysis of this functional group.

The formation or the hydrolysis of an acetal function proceeds by the mechanism described in Fig. 16 in which oxonium ions and hemiacetals occur as intermediates. It has also been established (76) that the rate determining step in acetal hydrolysis is generally the cleavage of the $C-O\lesseqgtr^{H}_{R}$ bond of the protonated acetal 100 to form the oxonium ion 111. This ion is then rapidly hydrated to yield the protonated hemiacetal 112 which can give the aldehyde product after appropriate proton transfers. It is pertinent therefore to find out if stereoelectronic effects influence the rate determining step (110 → 111) of this hydrolysis reaction.

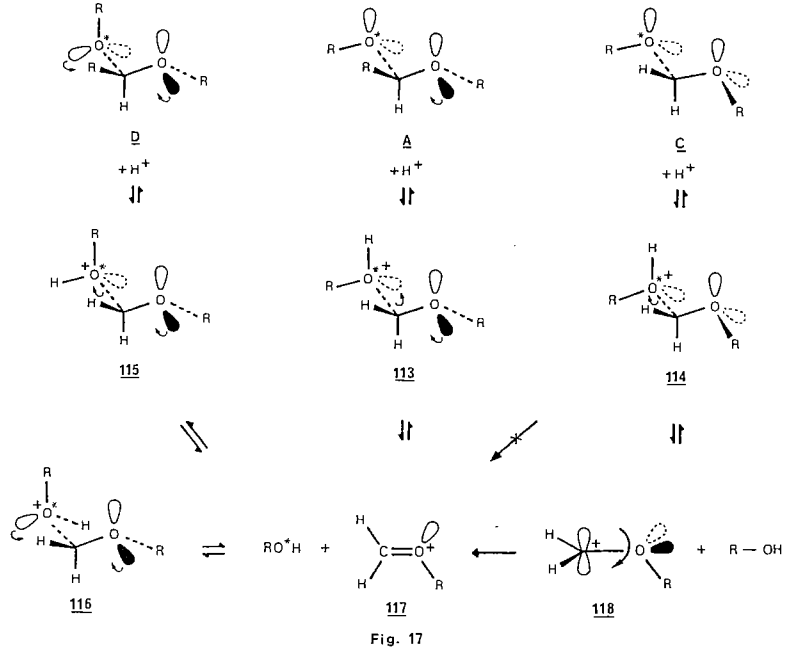
We will first examine what might occur when stereoelectronic effects are taken into account. An analysis of the conformations D, A, and C (Fig. 17) of dimethoxymethane which have two, one, and zero anomeric effects respec-



110 111 112

Fig. 16

tively, leads to the following predictions. The C − OR bond in conformer A should be shorter than a normal C − O ether bond because it has a partial double-bond character due to the anomeric effect, whereas the C − O*R bond



D A C

115 113 114

116 117 118

Fig. 17

should be longer than usual because of electron donation from the other oxygen. In conformer D, both C − O bonds have partial double-bond character; they could be shorter than normal. Since conformer C has no anomeric effect, its two oxygens are identical. The C − O bond lengths should be normal with a value intermediate to those predicted for conformer A.

Bond lengths collected from experimental data in X-ray crystal-structure determination of methyl pyranosides (11) and other products (77) strongly support the above discussion. Oxygen atoms with an electron pair antiperiplanar to a C − O*R bond definitely have shorter C − O bonds whereas the C − O*R bond is longer than normal. Interestingly, theoretical calculations have been carried out (11, 78) and the results are consistent with the above discussion and experimental observations.

As a consequence, stereoelectronic effects should also influence the basicity of the oxygen atoms of the acetal function, thence their relative ease of protonation. For instance, the oxygen atom of the O* − R group should be more basic than the other in conformer A. In conformer C which has no anomeric effect, the two oxygens are completely equivalent, and they should have a basicity intermediary to those of the oxygen atoms of conformer A. Since conformer D has two anomeric effects, both oxygens should be slightly more basic than the OR oxygen of conformer A.

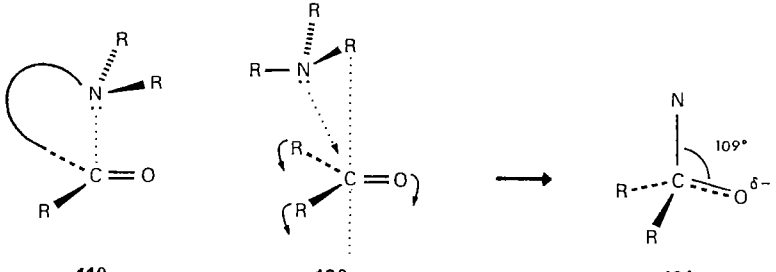
Consequently, by protonation of the O*R oxygen, the C − O*R bond length should increase to a larger extent in conformer A (→113) than in conformer C (→114) because the non-protonated oxygen of 113 has an electron pair antiperiplanar to the C − O*H R bond which is not the case with 114. With conformer D, protonation of the electron pair of the O*R oxygen which is antiperiplanar to the C − OR bond (→115) should lead to a situation similar to that of 113. On the other hand, protonation of the O*R oxygen can take place on the other electron pair (→116), and in this case, the C − O*H R bond length should not increase as much because in 116, the protonated oxygen has still an electron pair antiperiplanar to the C − OR bond. Thus, the stereospecific protonation of one of the two electron pairs of the O*R oxygen in conformer D leads to two completely different situations (115 and 116). This is very interesting because it points out the importance of the stereochemistry of protonation as well as the relative basicity of two electron pairs on the same oxygen atom. For instance in conformer D, the electron pair of the O*R oxygen which is not engaged in an anomeric effect should be more

basic than the other and on that basis, protonation of D should give 116 in preference to 115.

An ab initio study on four different conformations of protonated dihydroxymethane has been carried out (78, 79). Comparison of these results with those obtained from the corresponding neutral conformations indicates that bond length and overlap population show strong stereoelectronic conformational dependence in complete agreement with the above discussion.

We can now examine the cleavage of the $C-O^{*}\overset{H}{\underset{R}{<}}$ bond in the protonated species 113, 114, 115, and 116. Intermediates 113 and 115 can undergo cleavage with the help of an electron pair from the neighboring oxygen atom to give the oxonium ion 117 and alcohol. In 116, a similar situation occurs, but the ejection of RO*H should be more difficult because the oxygen atom of the leaving group still has an anomeric effect. Conformer 114 cannot break down with the help of an electron pair to give directly the delocalized ion 117; it should give first the high energy undelocalized cation 118 which can be transformed into the more stable oxonium ion 117 after a rotation of 60° of the C − OR bond. If the energy difference between the processes 114 → 118 → 117 and that of 115 → 117 or 113 → 117 is such that the former cannot compete with the others, the acetal hydrolysis will be said to take place under stereoelectronic control.

As a consequence of the principle of stereoelectronic control, the reverse process, i.e. the addition of an alcohol to an oxonium ion (e.g. 117 → 113) must take place through a precise pathway. Evidence on this pathway comes from the X-ray analysis (80, 81) of molecules containing an amino group and a carbonyl group in close proximity (e.g. 119) (see also (82)).

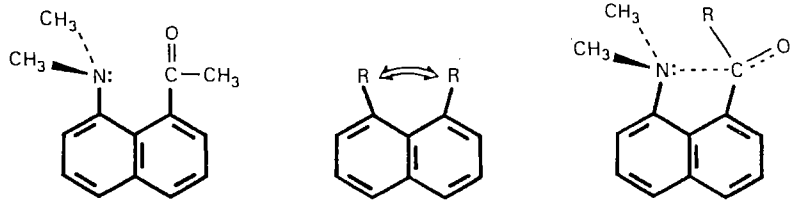


119 120 121

Bürgi, Dunitz, and Shefter (80) made the following observations: the N:···C=O distance was found too long for a bond but much too short for no-bonding, the RRC = O unit (120 → 121) deviates from its usual coplanar geometry and the probable orientation of the electron pair of the approaching nitrogen is assumed (this cannot be observed) to lie close to the local threefold axis of the tertiary amino group. This analysis clearly indicates an interaction between the nitrogen atom and the carbonyl group. The crystal structures leave no doubt that the nucleophile approaches the carbonyl along a vector at an angle close to 109° with the C=O bond. As the nucleophile approaches the carbonyl carbon, the oxygen atom and the alkyl substituents bend out the plane and the carbon oxygen bond length increases (cf. 120 → 121).

SGF-LCGO calculations for the nucleophilic addition of hydride ion to formaldehyde to yield methanolate anion ($H^- + CH_2=O \rightarrow CH_3O^-$) have been carried out (83, 84). Interestingly, the calculated reaction path for this reaction shows striking similarities to that derived from structural correlations for amine addition to a ketone function.

Strong evidence for the reaction path of the addition of a nucleophile to a carbonyl group comes from the X-ray structure of the naphthalene amino ketone 122 (85). In most 1,8-disubstituted naphthalenes, both substituents are splayed outward (cf. 123). In 122, the C − CO bond is splayed outward, but the C − N bond leans inward (cf. 124). This brings the nitrogen into a more favorable position for attack than is possible in the undistorted molecule. Similar observations were made with the amino ester (122, $COCH_3$=$COOCH_3$) and the amino carboxylic acid (122, $COCH_3$=COOH).

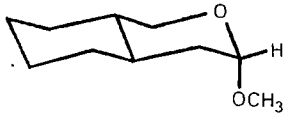


122 123 124

Capon and Thacker (86) have provided good evidence that the isomerization of methyl α and β-glucopyranosides in acidic methanol proceeds by the ejection of the methoxyl group to give the glucopyranosyl cation. The hydrolysis

of these compounds should also proceed in a similar manner to give the same cation which is captured by water to yield the hydrolysis product (87, 88). Since the ejection of a methoxy group can take place with the help of an electron pair in the case of α-glycosides only, the α-anomers should hydrolyze at a faster rate than β-anomers.

Early studies on the relative rate of acetal hydrolysis described in the literature bring no evidence in favor of stereoelectronic control. Feather and Harris (89) have studied 10 anomeric pairs of alkyl glucopyranosides, and found that the β-anomers containing the equatorial methoxy group hydrolyzed more rapidly (1.3-3.2 times faster) than the α-anomers with the axial methoxy group. BeMiller and Doyle (90) have observed similar results by measuring the rate of hydrolysis of 11 anomeric pairs of alkyl glucopyranosides. In the case of aryl glycosides, the α-anomers hydrolyzed slightly more rapidly (91). Van Eikeren (92) has prepared the conformationally rigid model compounds 125 and 126 and found a relative rate of hydrolysis of 1.5 in favor of the axial isomer 125.



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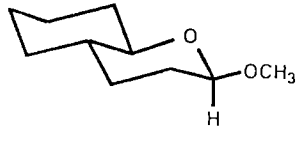
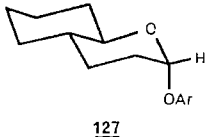


126

Chandrasekhar and Kirby (93) have observed that the hydrolysis of the axial p-nitrophenoxy isomer 127 is pH-independent in the pH range 7-10 and found that the rate of this spontaneous hydrolysis is 3.3 times slower than the equatorial isomer 128 under the same conditions. Thus, in a system designed to eliminate all other factors, including the problems of interpretation associated with acid-catalyzed reactions, no evidence was found that acetal cleavage is subject to stereoelectronic control.



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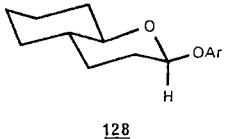

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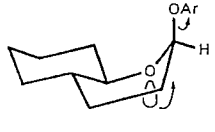
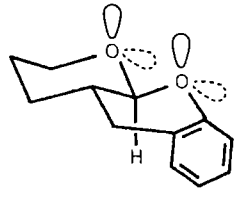


129

A conclusion can therefore be reached that electronic effects are not important in the rate of hydrolysis of acetals, but this is valid only if these compounds hydrolyze in their ground state conformation. The reality could well be completely different. For instance, an acetal could prefer to hydrolyze with stereoelectronic control via a higher energy conformation. Thus, the hydrolysis of 127 and 128 could occur with stereoelectronic control at a more or less competitive rate. Compound 127 would hydrolyze via its ground state conformation whereas 128 would hydrolyze via the boat conformation 129. This situation is possible because the enthalpy of activation for the cleavage of the 4-nitrophenoxy group in 127 and 128 is close to 25 kcal/mol, a much greater value than the barrier for the formation of the boat conformation 129 which is of the order of 10 kcal/mol (94). Therefore, 129 could lie on the reaction coordinates.

The first experimental evidence that acetal hydrolysis is controlled by stereoelectronic factors was provided by Kirby and Martin (94). They have measured the rates of the acid catalyzed hydrolysis (0.1 N HCl) of the tricyclic acetal 130 which has no electron pair antiperiplanar to the leaving group, and the corresponding cis isomer 131 which does have an electron pair properly oriented to eject the leaving group. They found that the cis isomer 131 was rapidly hydrolyzed whereas the trans isomer 130 in which the conformation of the acetal centre is locked, was still not completely hydrolyzed after several weeks, indicating a difference in rate of at least 3000.



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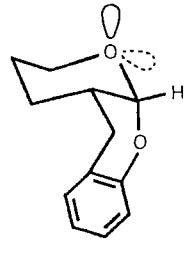
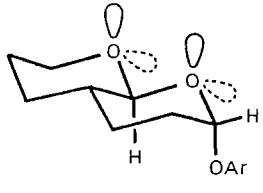


131

They also found that at pH 9, 130 was hydrolyzed 3.4 times more slowly than 131. It was shown, however, that the rate determining steps are not the same. In 130, it is the C—O bond cleavage whereas in 131, it is the hydration of the corresponding oxonium ion. Consequently, a direct comparison between the rates of the spontaneous hydrolysis of 130 and 131 cannot be

made. However, 130 can be compared with trans bicyclic acetal 128. They both have essentially the same equatorially oriented leaving group in the ground state and they are hydrolyzed by a rate determining C—OAr cleavage at pH 9. The only difference is that 128 can adopt the boat form 129 whereas 130 cannot take a similar conformation. Compound 128 at 39°C is hydrolyzed 20 times faster than 130 at 100°C, which is equivalent to a factor of over 10^4. Kirby and Martin (94) concluded that this rate difference is a direct consequence of the rigid geometry of 130. Indeed, 130 has no reasonable accessible conformation with an electron pair antiperiplanar to the leaving group. The stereoelectronic barrier to the C—O bond cleavage was consequently estimated to be almost 7 kcal/mol.

A further example of stereoelectronic control in acetal cleavage was also discovered by Kirby and Martin (95) who studied the spontaneous hydrolysis of the axially oriented p-nitrophenoxy acetals 132 and 133. Loss of p-nitrophenolate from these compounds would generate the oxonium ion 134, an acetal with a much better leaving group, i.e. the aldehyde oxygen. If one of the electron pairs on the oxygen atom of ring A in 134 is in a position to participate, it should trigger a concerted reaction to form 135 directly. Such participation is possible only in the case of the cis isomer 133. So, the rate of hydrolysis of the trans isomers 132 should be much slower.



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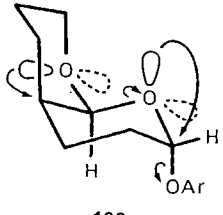

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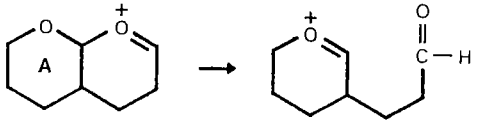
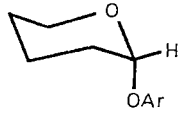


134 135



136

The experimental results are consistent with this expectation. The spontaneous hydrolysis of trans isomer 132 is 1380 times slower than that of p-nitrophenoxytetrahydropyran (136), while the cis isomer 133 is hydrolyzed ≈7 times more slowly than 136. The enthalpy barrier associated with stereoelectronic control in the trans isomer 132 was estimated to be 7.2 kcal/mol, a value identical to that obtained for compound 130.

Following the approach pioneered by Bürgi and Dunitz (80, 96), Jones and Kirby (97) further discovered a linear relationship between bond length and reactivity. They first determined crystal and molecular structures for a series of 2-substituted aryloxytetrahydropyran derivatives (98 - 101). I have previously pointed out that these compounds are hydrolyzed spontaneously by way of an oxonium ion and the crystal structures show that differences in bond length are already present in the ground state. They found that in axially oriented aryloxytetrahydropyrans, the endocyclic C—O bond is significantly shortened and the C—OAr bond of the leaving group lengthened, by an amount which depends on the electronegativity of the O-Aryl oxygen atom. They further noticed that this variation in bond length is very simply related to the rates of hydrolysis of these acetals. Indeed, the rates of hydrolysis show a linear dependence with the pKa of the leaving group when the C—O cleavage is rate determining (102, 103). A plot of bond length against the pKa of the leaving group is equivalent to a plot against the free energy of activation for C—O cleavage in water. This plot shows that the length of the two C—O bonds of the acetal group depend linearly on the pKa of the leaving group. In this manner, they could predict that the C—OCH_3 bond length for a typical axial methyl glycopyranoside should be 1.401 Å, a value identical, within experimental error, to the observed mean value of 1.405 Å obtained by X-ray analysis (54).

The first experimental evidence that there is stereoelectronic control in the formation of an acetal function was recently obtained (23) by studying the mild acid cyclization of bicyclic hydroxypropyl acetal 137 (Fig. 18). At room temperature, compound 137 gave only the cis tricyclic acetal 138; the appearance of a small quantity of the trans tricyclic acetal 139 occurred only after 5 days. On the other hand, when the cis acetal 138 was refluxed under the same conditions, isomerization took place to yield an equilibrium mixture of cis (45%) and trans (55%) acetals 138 and 139.

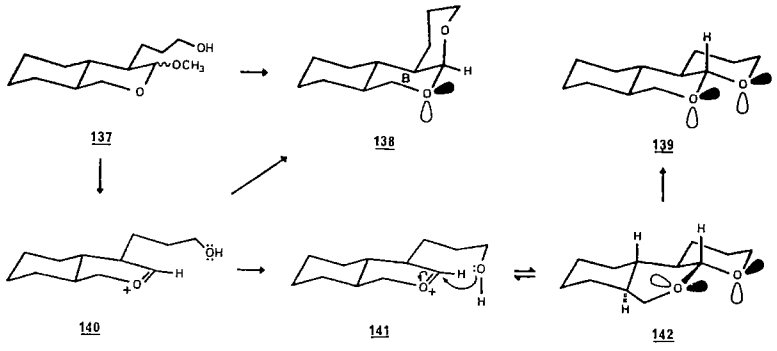


Fig. 18

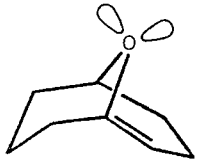
The specific conversion of 137 into the cis tricyclic acetal 138 is clearly the result of a kinetically controlled reaction. As a consequence, the formation of trans acetal 139 must involve a higher energy barrier than that of cis acetal 138. The first step in the cyclization reaction must be the loss of methanol from the starting material 137 to give the cyclic oxonium ion 140. The hydroxyl group has then the choice of attacking the β or the α-face of the oxonium ion 140 to give the cis or the trans tricyclic acetals 138 and 139 respectively. It can be readily seen that the β-attack on 140 can give the cis acetal 138 with stereoelectronic control, because the oxygen of ring B in 138 has an electron pair oriented antiperiplanar to the newly formed C − O bond. On the other hand, the α-attack on 140 with stereoelectronic control cannot yield the trans acetal directly in its more stable conformation 139. The α-attack (i.e. 141) must first give conformer 142 of the trans acetal having its ring B in a boat form in order to have the oxygen atom of ring B with an electron pair antiperiplanar to the newly formed C − O bond. 142 would then undergo a conformational change to the more stable conformation 139 of the trans acetal. Clearly, the transition 140 → 141 → 142 → 139 requires more energy than the transition 140 → 138, a conclusion which is in accord with the experimental result.

In a more recent study (104), similar results were obtained with the bicyclic thiol hemiacetal 75 (Fig. 13). Cyclization of 75 under kinetically controlled conditions gave the cis monothioacetal 76; the trans isomer 77 was not observed. Thus the attack of an SH group on a cyclic oxonium ion must also take place preferentially with stereoelectronic control.

These recent results obtained with compounds in which the acetal function is locked in a specific conformation clearly demonstrate that stereoelectronic factors are important in connection with the reactivity of acetals. Stereoelectronic effects must therefore play a role in compounds where the conformation of the acetal function is not fixed. On that basis, it seems quite clear that α-glycosides must hydrolyze via their ground state conformation whereas β-glycosides must first assume a boat conformation in order to fulfill the stereoelectronic requirement. Interestingly, van Eikeren (92) in his study on the relative rates of hydrolysis of axial and equatorial bicyclic isomers 125 and 126 has obtained results which indicate that the anomers hydrolyze via different transition states. Moreover, the transition state of the axial anomer would involve more extensive C − O bond breakage than that of the equatorial anomer. This is in complete accord with the above conclusion concerning α and β-glycosides, since it is conceivable that, in the cleavage of a C − OR bond at the anomeric center, the C − OR bond will be longer in the transition state when the molecule exists in a chair rather than a boat form because the chair form is at a lower energy level.

It is well known that in lysozyme-oligosaccharide complexes (105-108), the pyrane ring derived from β-glycosides is distorted from the normal chair conformation toward a half-chair conformation. This distortion raises the energy of the ground state of the substrate and thus lowers the energy of activation for bond cleavage. Thus, in the hydrolysis of β-glycosides by lysozyme, hydrolysis would take place via a distorted substrate and that would be mainly for stereoelectronic reasons.

Chwang, Kresge, and Wiseman (109) have made the interesting observation that the bridged vinyl ether 143 is hydrated (at the bridgehead carbon) more slowly than 144 by a factor of 10^2, even though hydration of vinyl ethers is normally faster than that of analogous olefins by a factor of 10^{5-8}. The sulfur analog (143, O=S) was found to be even less reactive than 144. These remarkable results can be readily explained by the fact that the electron pairs on the oxygen (or sulfur) atom are not properly aligned to give a delocalized oxonium ion (cf. 117). The oxygen electron pairs are orthogonal to the π system of the double-bond; protonation of 143 must therefore yield a high energy undelocalized cation which is further destabilized by the inductive effect of the oxygen atom (cf. 118). The overall rate of the hydration reaction is thus considerably reduced.



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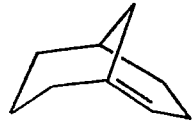
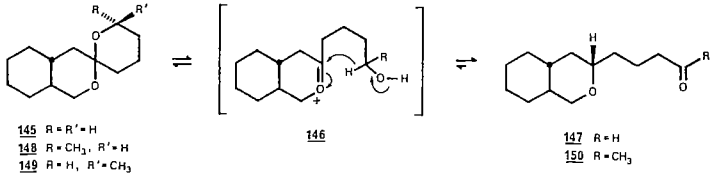


144

Hydride transfer to cyclic oxonium ion

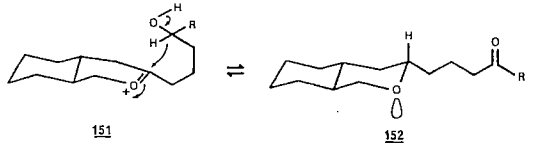
We should also expect stereoelectronic control when the hydroxyl group is replaced by another nucleophile in the reaction with cyclic oxonium ions. A recent report (110) shows that hydride transfer to cyclic oxonium ion is subject to stereoelectronic control. Tricyclic spiroketal 145 (Fig. 19) undergoes an acid-catalyzed oxidation-reduction reaction to give the equatorial bicyclic aldehyde 147 stereospecifically. Similarly, spiroketals 148 and 149 gave the corresponding equatorial bicyclic ketone 150.



145 R=R'=H
148 R=CH_3, R'=H
149 R=H, R'=CH_3

146

147 R=H
150 R=CH_3



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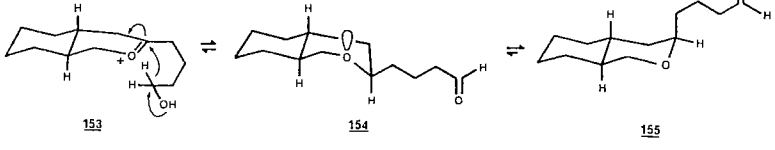


153

154

155

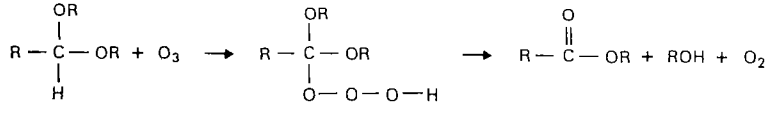
Fig. 19

These results are interpreted by invoking an internal hydride transfer from an alcohol function to the cyclic oxonium ion (i.e. 146) (111). It can be readily seen that the β-attack on 146, i.e. 151 can occur with stereoelectronic control yielding 147 and 150 in their most stable conformation 152. On the other hand, the α-attack on 146, i.e. 153 must first give conformer 154 having its ring B in a boat form in order to fulfill the electron pair alignment requirement. Conformer 154 would then give the more stable conformation 155 of the corresponding axial isomer. The transformation 153 → 154 → 155 requires more energy than 151 → 152; thus, the equatorial isomers 147 and 150 are the sole products of these transformations.

This rationalization indicates that internal delivery of a hydride is not a requisite for the observed stereospecificity. Reduction of the oxonium ion with an external hydride reagent should also give equatorially oriented bicyclic ether only. Accordingly (112), reduction of tricyclic spiroketal 145 with sodium cyanoborohydride at pH ≈3-4 yields only the equatorial bicyclic ether alcohol (147, CHO≡CH_2OH). Eliel and co-workers (113) have previously suggested that the orientation of the electron pairs of oxygen atoms influence the course of the reduction of 2-alkoxytetrahydropyran with lithium aluminium hydride-aluminium trichloride.

Oxidation of the C—H bond in acetals

In 1971, it was discovered that ozone reacts in a completely specific fashion with the acetal function derived from an aldehyde to give the corresponing ester and alcohol (114). This reaction proceeds via the insertion of ozone into the C—H bond of the acetal forming a hydrotrioxide intermediate (156) which breaks down to yield the reaction products, the ester, the alcohol and singlet oxygen (115, 116). The hydrotrioxide intermediate 156 can be detected at low temperature (115).



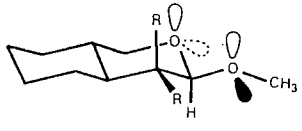
156

In the course of a study on the generality of this reaction (117), it was found that the rates at which different acetals are oxidized vary considerably and this led to the proposal that the reaction is controlled by stereo-

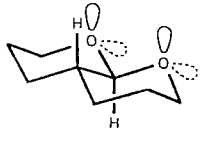
electronic factors. Basically, it was proposed that in order for oxidation to proceed, it is required that one non-bonded electron pair on each oxygen atom lie antiperiplanar to the C—H bond of the acetal function.

A study (118, 119) on the reactivity of a series of appropriate chemical models did confirm this postulate. Conformers A, C, and F of an acetal function (Fig. 1, p. 4) possess on each oxygen atom an electron pair oriented antiperiplanar to the C — H bond, conformers B and D have only one oxygen with an electron pair properly oriented whereas conformer E has none. Thus, conformers B, D, and E should be inert and conformers A, C, and F should be reactive towards ozone.

Conformationally rigid β-glycosides were found to be reactive towards ozone. At least one of the rotamers E_1, E_2, and E_3 of a β-glycoside (Fig. 9) which corresponds to conformers A, B, and C respectively of an acetal function should therefore be reactive. Compounds 157 and 158 are rigid model compounds for rotamers E_1 and E_3. These two compounds react with ozone; thus, conformers A and C are reactive conformers. On the other hand, the unreactive compound 159 is a rigid model for rotamer E_2; thus, conformer B is not reactive, as predicted.



157 R = CH_3



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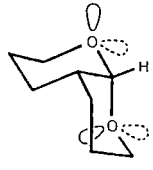
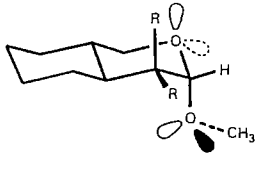
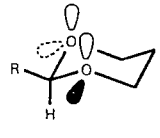


159

Conformationally rigid α-glycosides were found to be inert toward ozone. Rotamers A_1, A_2, and A_3 of an α-glycoside which correspond to conformers D, B', and E respectively of an acetal function are consequently unreactive as predicted. Compound 160 can be considered a rigid model for the most stable rotamer A_1 (conformer D) of an α-glycoside and it was found unreac-



160 R = CH_3



161

tive. Finally, 1,3-dioxanes 161 which are rigid models for conformer F were smoothly oxidized.

This analysis was supported by the fact that conformationally labile α-glycopyranosides were found to react with ozone. Similar results were also observed with α and β-glycofuranosides as these compounds are not maintained in a rigid conformation.

Interestingly, acyclic (dialkoxy) acetals react with ozone at a much slower rate than cyclic acetals such 1,3-dioxanes 161. It was proposed (118) that the low rate of oxidation of acyclic acetals is due to the fact that they exist in the conformation D (Fig. 1) which is not reactive. Thus, acyclic acetals would first undergo a conformational change from conformer D to either conformer A, C, or F before reacting with ozone. The fact that a large percentage of acyclic acetals exist in the non-reactive conformation D lowers the effective concentration and the rate of oxidation is affected accordingly. Also, conformer F of cyclic acetals might be at a higher energy level, thus more reactive, than the conformations A or C which can be taken by acyclic acetals.

Taillefer and co-workers (120) have undertaken an interesting kinetic study of cyclic and acyclic acetals. They found that the enthalpy of activation is remarkably low (about 5-7 kcal/mol) for cyclic and acyclic acetals, whereas the entropy of activation was found to be very high and negative, indicating a highly ordered transition state. They also showed that the two different types of acetals behave differently toward ozone. They observed an isokinetic relationship for acyclic acetals and the isokinetic temperature was found to be below the experimental temperature range, a domain where reactivity is dominated by entropy factors. These results contrasted with those obtained for cyclic acetals where the isokinetic temperature falls above the working temperatures, a domain of temperatures where reactivity depends mainly on enthalpy factors. These results and the above rationalization constitute rather strong experimental evidence that a conformational change before oxidation must take place in the case of acyclic acetals.

It is clear from the above results that the oxidation of the acetal function is controlled by stereoelectronic factors. The next step is to try to understand how these electronic effects operate to lower the energy barrier of the oxidation reaction.

The experimental evidence obtained (116, 117) indicates that the central carbon of the acetal function becomes positively charged during the oxidation step. Furthermore, a rather high primary isotope effect ($k^H/k^D = 6.5$) has been measured (121). These results indicate that the reaction mechanism proceeds either via a direct hydride transfer yielding a dialkoxycarbonium ion and a hydrotrioxide ion which would collapse to the hydrotrioxide intermediate (162 → 163 → 165) (Fig. 20), or via an insertion of ozone in a 1,3-

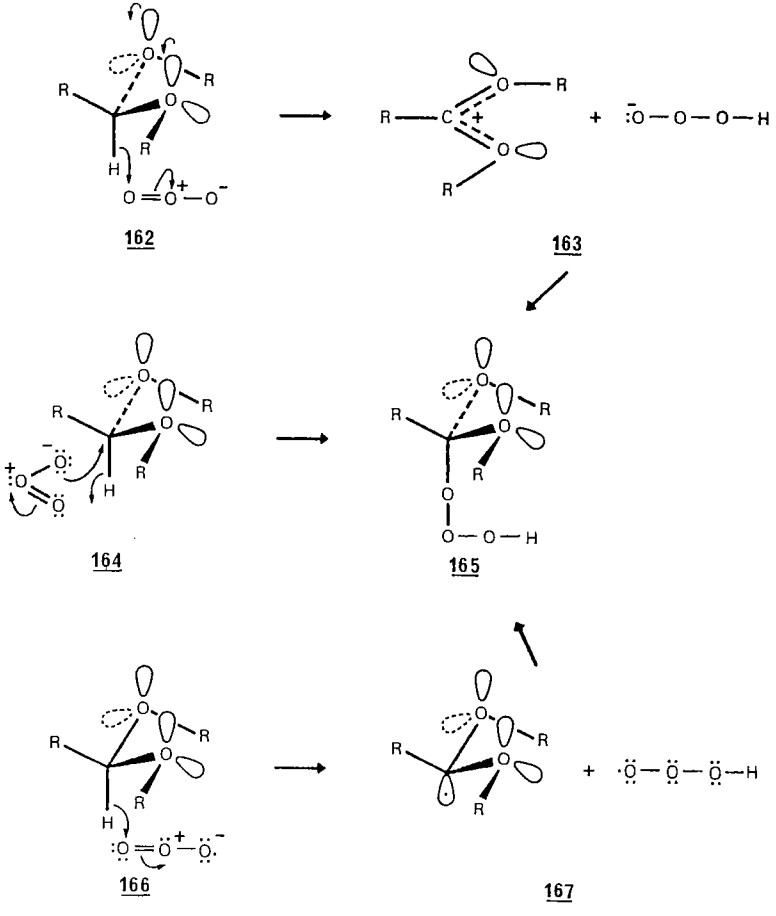
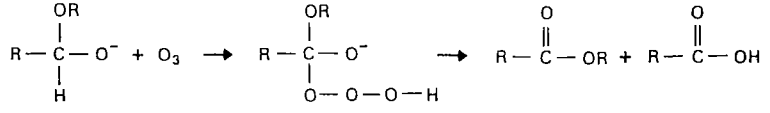


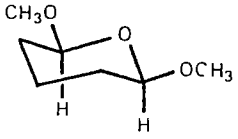
Fig. 20

fashion into the C − H bond of the acetal function (164 → 165). If this is the case, the need for an electron pair antiperiplanar to the C − H bond for each oxygen atom of the acetal function becomes clear. Antiperiplanar electron pairs should increase the electron density of the C − H bond which would then be more easily attacked by an electrophile like ozone. An ab initio study carried out by Lehn, Wipff, and Bürgi (78) is in accord with this conclusion. This effect should also stabilize the incipient dialkoxycarbonium ion 163, if it is formed. This rationalization is in agreement with the fact that negatively charged hemiacetal oxy anion 168 reacts more rapidly than dialkoxyacetals with ozone (122). The product of the reaction is a mixture of the corresponding carboxylic acid and ester which presumably come from the two possible modes of cleavage of intermediate 169.



168 169

It is also possible that the formation of the hydrotrioxide intermediate occurs via a radical mechanism (166 → 167 → 165). This implies that a radical would be more stable when there are two electron pairs on adjacent oxygens oriented antiperiplanar to it. There is evidence in the literature that this is indeed the case. Bernasconi and Descotes (123) have observed a preference for axial hydrogen abstraction of cis and trans 2,6-dimethoxytetrahydropyran by photolysis of benzophenone; the cis isomer 170 was photodegraded more rapidly than the trans isomer 171. Hayday and McKelvey (124) found that, at ambient temperature, triplet benzophenone abstracted the axial hydrogen from cis-2-methoxy-4-methyltetrahydropyran (172) about 8 times faster than it abstracted the equatorial hydrogen from the trans isomer 173. Since both compounds gave the same product distribution it was concluded that a common free radical was formed. This was subsequently confirmed (125) by using EPR spectroscopy to identify 2-alkoxytetrahydropyran-2-yl radicals generated from conformationally rigid cis and trans precursors. The tert-butoxyl radical was also shown to exhibit a strong (12 fold) preference at room temperature for the removal of the axial over the equatorial hydrogen of the anomeric carbon, with conformationally rigid pairs of 2-methoxy-1,3-dioxanes and 2-methyl-1,3-dioxanes (125).



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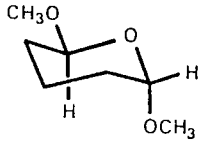

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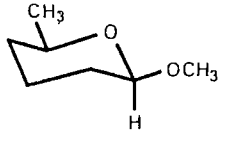

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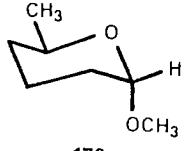
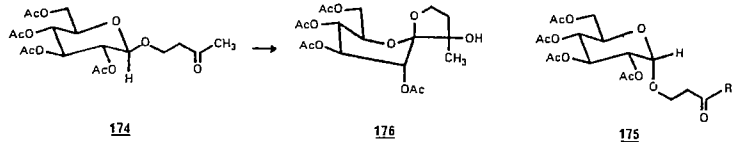


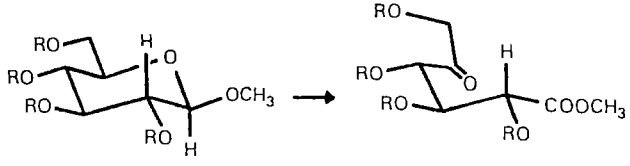
173

In a more recent study on the relative rates of hydrogen atom abstraction by photogenerated tert-butoxyl radical on a variety of cyclic and acyclic ethers, acetals, and orthoformates, Malatesta and Ingold (126) observed a pronounced stereoelectronic effect which produces high rates of abstraction from those C−H bonds which had adjacent oxygen with appropriate electron pair orientation. When the C−H bond had adjacent oxygen with improperly aligned electron pair, abstraction was very much slower. Similar results were observed by Beckwith and Easton (127) with substituted 1,3-dioxanes. The conversion of acetals to lactones by radical abstraction where there would be a stereoelectronic control in bond cleavage has also been reported (128). Remy, Cottier, and Descotes (129) have reported the photolysis of the α and β-isomers 174 and 175. With the β-anomer 174, the reaction is complete in 40 h and yields the spiro compound 176. With the α-anomer 175, the reaction is slow and does not lead to the formation of a specific product.

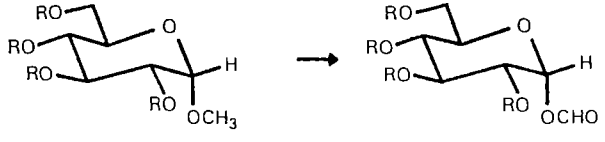


174 176 175

The oxidation of aldehyde acetals to esters has also been reported with various agents such as N-bromosuccinimide (130-135), triethyloxonium (136, 137) or triphenylmethyl tetrafluoroborate (138). It has not yet been verified if these reactions are controlled by stereoelectronic effects. Angyal and co-workers made an interesting observation in the course of their study (139-143) on the oxidation of acetals derived from carbohydrates with chromium trioxide in acetic acid. They found (139) that α and β-glycosides react differently with this reagent. With β-glycosides, the anomeric hydrogen is first oxidized and the product obtained is the ketoester (177 → 178) whereas, with α-glycosides, the methyl group is slowly oxidized to give the formate (179 → 180). Stereoelectronic effects must again play a role in these two reactions.



177 178



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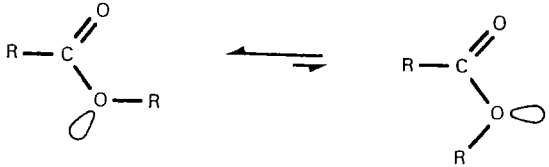
CHAPTER 3

ESTERS AND RELATED FUNCTIONS

Stereoelectronic effects and the ester function

This Chapter deals with the stereoelectronic effects which control the cleavage of tetrahedral intermediates during the formation or the hydrolysis of an ester. Since these effects are also operative in the ester function itself, a discussion of the functional group will first be presented.

In the ester function, it was proposed that two types of electronic effects referred to as the primary and the secondary electronic effects (1-3), are present. The role and the relative importance of these two types of electronic effects can be understood by analyzing them in relation to the geometry and the relative stability of the two forms, Z and E, of the ester function.

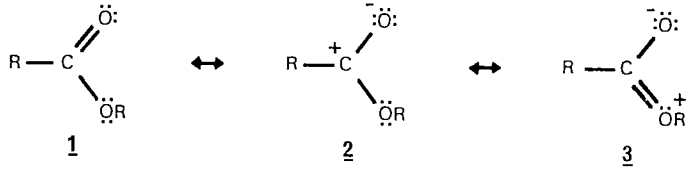


Z E

It is well known that esters are planar and that the Z form is much more stable (≈ 3 kcal/mol) than the E form (4). The E form is of course observed in small ring lactones but as soon as the size of the lactone ring allows the Z form to exist, the E form is no longer observed (5). Even in the case of tert-butyl formate, where there must be a strong steric repulsion

between the carbonyl oxygen atom and the tert-butyl group in the Z form, this form still predominates (≈90%) (6, 7).

The primary electronic effect is due to the delocalization of electron pairs between the ether oxygen and the carbonyl group of the ester function as expressed by the resonance structure 1, 2, and 3. Resonance structures 1 and 2 show the delocalization of an electron pair between the carbon and oxygen of the carbonyl group (1 ↔ 2) and resonance structures 2 and 3 show that the ether oxygen has one electron pair delocalized towards the same central carbon (2 ↔ 3). The primary electronic effect can therefore be viewed as the result of two n-π* interactions. The three atoms involved can be considered to be sp^2 hybridized and on that basis, the three-dimensional representations 4 and 5 correspond respectively to the Z and E forms of the ester function.



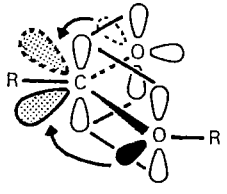
1 2 3

4 (Z) 5 (E)

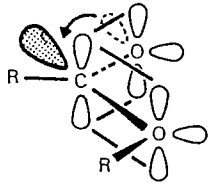
The secondary electronic effects in the ester function are essentially similar to the anomeric effect discussed previously for the acetal function, involving an n-σ* interaction. The only difference is that the central carbon is trigonal (sp^2 hybridized) in esters and tetrahedral (sp^3 hybridized) in acetals.

The carbonyl oxygen in both the Z (4) and the E (5) esters has an electron pair oriented antiperiplanar to the C — OR bond, and an n-σ* interaction should therefore exist because this electron pair orbital can overlap with

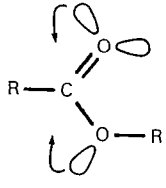
the antibonding orbital (σ^*) of the C—OR bond. In other words, this secondary electronic effect (or anomeric effect) should give a triple bond character to the carbonyl group ($\ddot{O}{=}C{-}\ddot{O}R \leftrightarrow {}^{+}\ddot{O}{\equiv}C\ \ddot{:}\ddot{O}R$). In the Z form (4), there is the possibility for another secondary electronic effect because, in this form, the ether oxygen has an electron pair which is oriented antiperiplanar to the C — O σ bond of the carbonyl group. This electron pair orbital can therefore overlap with the antibonding orbital (σ^*) of that bond. Thus, in Z esters, in addition to the primary electronic effect, there are two secondary electronic effects which are illustrated in three dimensions by 6 and in two dimensions by 7. In E esters, besides the primary electronic effect, there is only one secondary electronic effect as shown in three dimensions by 8 and in two dimensions by 9.



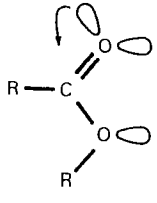
6



8



7

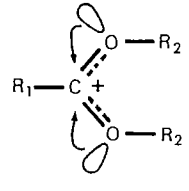


9

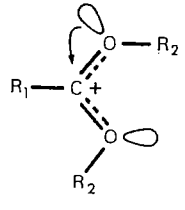
The additional stabilizing secondary electronic effect in the Z form might be larger than that (≈1.4 kcal/mol) observed in acetals, because the carbonyl bond in esters is a more polarized bond than the C — OR bond in acetals and therefore, the antibonding orbital of the σ C — O bond should be of lower energy allowing increased overlap. It has been postulated on that basis (1-3) that the greater stability of the Z form (≈3 kcal/mol) by comparison with the E form in esters would be due mainly to this secondary electronic effect.

Thus, primary electronic effects (n-π^* interaction) form the conjugated system of the ester function whereas secondary electronic effects (n-σ^* interaction) are the result of the orientation of non-bonded electron pairs antiperiplanar to the σ C — O bonds of the ester function. Clearly, the primary are energetically more important than the secondary electronic effects and this terminology is justified by the fact that these two effects have their origin in the same chemical principle, orientation in space of electron pairs with resultant electronic delocalization.

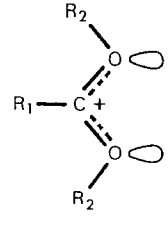
There is no direct experimental evidence to show the importance of the secondary electronic effects in the ester function except for the relative stability of the Z over the E form. However, the relative stability of the different forms of dialkoxycarbonium ions can be explained by considering these electronic effects. Since dialkoxycarbonium ions are alkylated derivatives of esters, the result can be used as evidence to support the importance of the secondary electronic effects in the ester function. It is known from X-ray evidence and supported by calculations (8, 9) that dialkoxycarbonium ions like esters are planar and that they can exist theoretically in three different forms, the ZZ (10), the EZ (11), and the EE (12) forms. The two oxygens of 10 each have one non-bonded electron pair antiperiplanar to a polar C — O bond, 11 has one, whereas 12 has none. Thus, 10, 11, and 12 have respectively two, one and zero secondary electronic effects, and on that basis, their relative stability should follow in this order. In the ZZ form (10), there is a severe steric repulsion between the two R groups; thus, with the exception of cases where the two R groups are part of a ring, this form must be eliminated. The EZ form (11) must therefore represent the most stable form of dialkoxycarbonium ions.



10



11

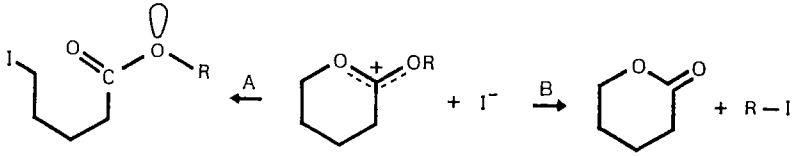


12

Ramsey and Taft (10) have provided the first evidence by nmr spectroscopy that the dimethoxycarbonium salt of methyl acetate exists in the EZ form (11) only. It was later found that at -30 to -80°C, there is predominance

(11, 12) of the EZ form, while at 0-38°C, both the EZ and the EE forms exist. The relative percentage of the EE form 12 depends on the nature of the substitutents. When R_1=H and R_2=alkyl, the EZ form predominates to the extent of 70-90%, and when R_1=R_2=alkyl, the EZ form becomes exclusive. Protonated esters (13) and acids (14-17) exist also in the EZ form, preferentially.

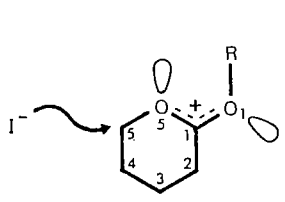
Further support for the importance of secondary electronic effects has recently been obtained (2, 18) from a study of the SN_2 displacement by iodide on lactonium salts. It was found that the iodide ion reacts instantly with salts such as 13 to give a mixture of iodoester 14, lactone 15, and alkyl iodide. For example, in the case of 13 (R=CH_3), a mixture of iodoester 14 (R=CH_3) (70%), and δ-valerolactone (15) (30%) was obtained.



14 13 15

These experimental results show clearly that the formation of iodoester (process A) can compete effectively with the formation of lactone and alkyl iodide (process B). This is a priori a surprising result. In process B, two molecules are formed and the ring is not broken while in process A, only one molecule is formed and the ring is cleaved. On that basis, process A should require more energy than process B. Furthermore, in lactonium salts having a methoxy group, iodide displacement on the primary methyl group should be more facile than that on the secondary methylene group of the ring. This factor again favors the formation of lactone, yet important quantities of iodoester are observed. It is therefore clear that there must be a new parameter which operates in process A only, lowering the energy of its transition state, so that it can compete with process B.

Assuming that these lactonium salts exist in the EZ form 11, the two transition states yielding 14 and 15 can be illustrated by 16 and 17 respectively. In 17, the bond to be broken is antiperiplanar to the non polar C_1-C_2 bond whereas in 16, the bond to be broken is antiperiplanar to the C_1-O_1 polar bond. In other words, in 16 the electron pair orbital of the C_5-O_5



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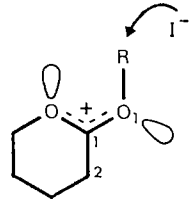


17

bond can be delocalized by an interaction with the antibonding orbital (σ*) of the polar C_1-O_1 bond whereas in 17, the electron pair orbital of the $R-O_1$ bond cannot be delocalized into an antibonding orbital of a polar C–O bond. Thus, the former process should be favored electronically over the latter and on that basis, rationalization of the experimental results becomes clear. These results can therefore be considered as further support for the importance of secondary electronic effects in the ester function.

Now that the electronic effects in the ester function have been explained in detail, we can examine the formation and the cleavage of tetrahedral intermediates derived from esters by applying the theory of stereoelectronic control for hydrolytic reactions, which was put forward in 1972 (19). According to this theory, in order to be favored, nucleophilic attack on esters must be perpendicular (≈109° according to ref. 20) to the plane at the conjugated system and give rise to a tetrahedral intermediate where the two oxygen atoms have each a lone pair oriented antiperiplanar to the newly formed bond. Following this rule, a Z ester (4) with a nucleophile Y must give intermediate 18 (Fig. 1) whereas an E ester (5) must give intermediate 19. Examination of the process 4 → 18 indicates that the conformation of the Z ester is transposed into the tetrahedral intermediate since the C–R and the O–R bonds which are antiperiplanar in 4 remain antiperiplanar in 18. Similarly, in the process 5 → 19, the two R groups which are syn in the E ester assume a gauche orientation in the intermediate 19. At the same time, the conversions 4 → 18 and 5 → 19 follow the principle of least motion (21-23).

According to the principle of microscopic reversibility, the reverse process must follow the same path. In fact, the stereoelectronic theory was first elaborated by examining this process, i.e. the cleavage of tetrahedral

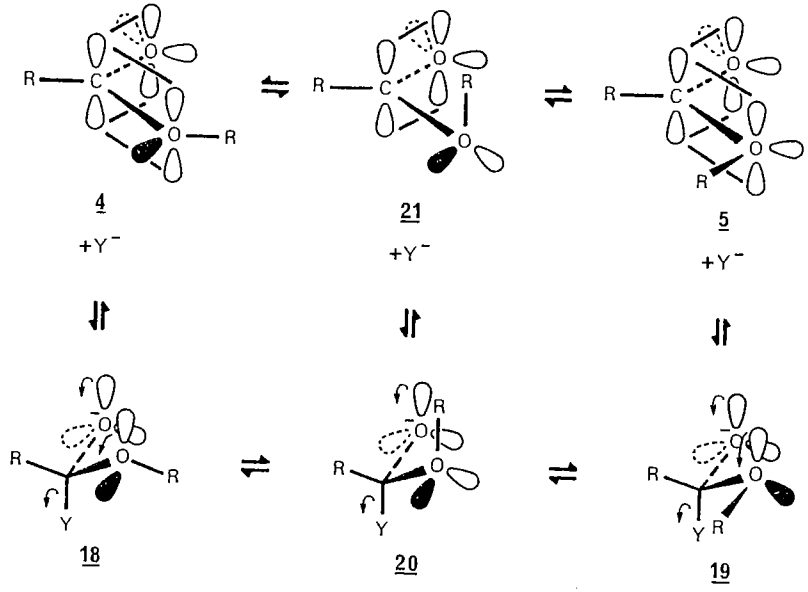


Fig. 1

intermediates. It was defined that the precise conformation of a tetrahedral intermediate must be transposed into the product of the reaction and the cleavage of a C − Y bond is allowed to take place with stereoelectronic control only if the two oxygen atoms of the tetrahedral intermediate have each an electron pair oriented antiperiplanar to the leaving group.

Intermediates 18 and 19 represent two of the three possible gauche conformers for the tetrahedral intermediate, and it is therefore pertinent to analyze the third gauche conformer which corresponds to 20. Intermediate 20 cannot cleave with stereoelectronic control because the OR oxygen does not have an electron pair properly oriented to eject the leaving group. Ejection of the leaving group in 20 could take place with the help of only one electron pair (from O^-), but it leads to 21, a non conjugated "ester" (lacking primary electronic delocalization). Intermediate 21 corresponds to the high energy intermediate which occurs during the thermal isomerization of Z and E esters. As the energy barrier for such interconversion is at least 15 kcal/mol (4), the energy difference between 21 and 4 (or 5) must be of that order. It is clear on that basis that the cleavage 20 → 21

is a much higher energy process than the cleavages 18 → 4 or 19 → 5.*

Intermediate 18 gives the most stable form (Z) of an ester whereas 19 yields the least stable form (E). An interesting question which follows is whether or not the energy barrier for the formation of a Z ester (18 → 4) is also lower than that for an E ester (19 → 5). An answer can be obtained from the analysis of the secondary electronic effects.

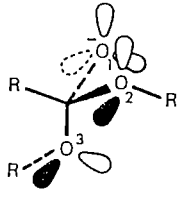
Interestingly, there is complete transmission of the electronic effects from the tetrahedral intermediate to the ester function in both processes. In intermediate 18, in addition to the two electron pairs which are antiperiplanar to the leaving group, each oxygen atom also has an electron pair antiperiplanar to a C − O bond. Thus, 18 has four secondary electronic (n-σ*) effects. However, in the cleavage of 18 which yields the Z ester 4, two of the secondary electronic effects become primary (n-π* interaction) effects (forming the π system) while the other two remain secondary effects (n-σ*). In intermediate 19, besides the two electron pairs which are antiperiplanar to the leaving group, the negatively charged oxygen also has one electron pair antiperiplanar to the C − OR group. Thus, 19 has three secondary electronic effects and its cleavage gives 5 where two of these secondary (n-σ*) electronic effects become primary (n-π*) while the third one remains a secondary electronic effect (n-σ*).

There is no gain or loss of electronic effects in either cleavage except that two secondary electronic effects (n-σ*) have been transformed into two primary electronic effects (n-π*) and on that basis, the energy barriers should be similar. However, since intermediate 18 has one extra secondary electronic effect by comparison with 19, the energy of the ground state of 18 should be lower than that of 19. Thus, in a situation where a tetrahedral intermediate would exist as a mixture of conformers 18, 19, and 20 which are rapidly equilibrating by rotation, the formation of the Z ester 4 would be favored. Consequently, under those conditions not only conformer 20, but also conformer 19 would not be able to compete with conformer 18 yielding the ester having the Z form 4. If it is indeed true,

*The energy barrier for the ejection of Y in 20 must also be higher than that for the corresponding hemiacetal (20, OR=R and Y=OR) because the inductive effect of the oxygen of the OR group in 20 creates a partial positive charge on the central carbon.

the cleavage of that intermediate will be said to take place with primary and secondary stereoelectronic control.

There are also situations where it is not necessary to have a conformational change in order to have two possible cleavages in competition. Such a situation is possible in a single tetrahedral intermediate when the leaving group Y is another OR group. For example, we can consider the three tetrahedral intermediates 22, 23, and 24.



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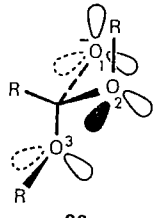
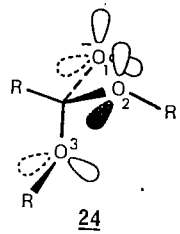


23



24

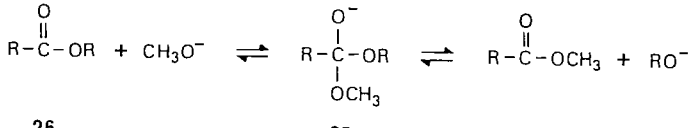
In intermediate 22, the R group of O_2 is oriented in such a way, that the cleavage of the $C-O_3$ bond will result in the formation of a Z ester. On the other hand, as the R group of O_3 is oriented antiperiplanar to the $C-O_2$ bond, cleavage of the $C-O_2$ bond cannot occur. It is therefore predicted that 22 will break down to give a Z ester by the cleavage of the $C-O_3R$ bond. In intermediate 23, the R group of O_3 is oriented in such a way to give an E ester by cleavage of the $C-O_2$ bond, and the cleavage of the $C-O_3$ bond cannot take place because the $R-O_2$ bond is antiperiplanar to the $C-O_3$ bond. Thus, 23 should give an E ester by ejection of the O_2R group.

The last example, intermediate 24, is more interesting because it can give either a Z or an E ester. Indeed, cleavage of the $C-O_3$ bond can yield a Z ester whereas cleavage of the $C-O_2$ bond would yield an E ester. Now that the two cleavages are possible in the same conformer, the argument used previously, i.e. the relative stability of different conformers, cannot be used to make a prediction in this case. However, it can still be predicted that the cleavage of the $C-O_3$ bond would be favored over that of the $C-O_2$ bond in 24 because the former leads to a product (Z ester) having two secondary electronic effects whereas the latter leads to a product (E ester) having only one. Consequently, the additional secondary electronic ($n-\sigma^*$) effect which lowers the ground state energy of the Z ester product

must also play a role in lowering the energy of the corresponding transition state which leads to its formation.

We have previously discussed, in the Chapter on acetals, the anomeric (or secondary electronic) effects as $n-\sigma^*$ interactions, and their influence on the leaving group ability of an OR group (cf. p. 32). Applying this principle to intermediates 22, 23, and 24 gives the following results. In 22, O_3 gives one secondary electronic effect (with $C-O_1$) and O_2 gives two (one with $C-O_1$ and one with $C-O_3$). As a consequence, the $C-O_3$ has one partial double-bond character whereas the $C-O_2$ bond has two; the O_3R group is thus a better leaving group than the O_2R group. This is therefore another argument in favor of the preferred ejection of the O_3R group in intermediate 22. In intermediate 23, O_2 and O_3 have each one secondary electronic effect; the O_3R and the O_2R groups must have similar leaving group ability. In intermediate 24, O_3 has one secondary electronic effect and O_2 has two. The O_3R group is thus a better leaving group, and its ejection should be easier than that of the O_2R group. This factor again favors the formation of a Z ester in preference to an E ester from intermediate 24.

On a more general basis, a hemi-orthoester intermediate such as 25 which has two different alkoxy groups can yield the two different esters 26 and 27, each having either a Z or an E conformation. Theoretically, the intermediate 25 can take the nine different gauche conformations described in Fig. 2, and the predicted stereoelectronically controlled cleavage for each conformation is indicated in Table 1. Conformer A (or F) has a conformation identical to that of intermediate 22. Similarly, conformer E (or G) corresponds to 23 and conformer B (or I) to 24. Conformer D cannot be cleaved; it is therefore predicted that the energy barrier for its cleavage must be higher than in the other cases. Conformers A, B, and C represent the three possible conformers resulting from the attack of methoxide ion on a Z ester. Similarly, conformers G, H, and I are the three possible conformers which can be formed from the reaction of methoxide ion with an E ester.



26 25 27

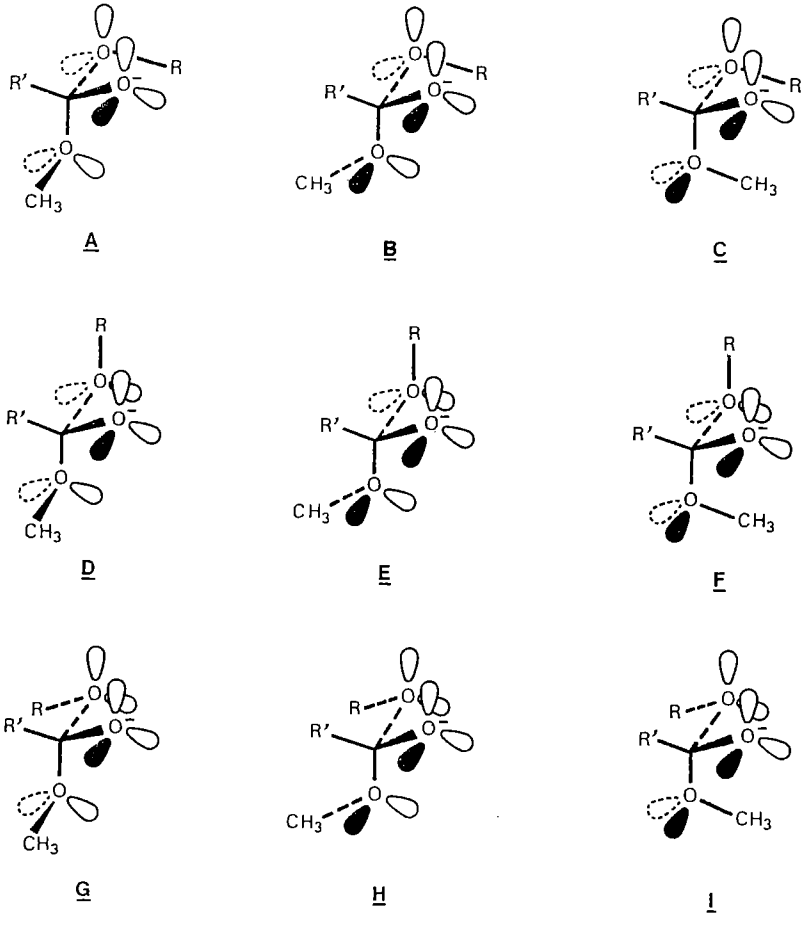


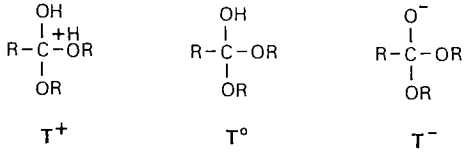
Fig. 2

The correlation between primary (n-π^* interactions) and secondary (n-σ^*) electronic effects in the cleavage of tetrahedral intermediates has now been explained in detail. Before attempting the rationalization of experiments which could potentially support the importance of the stereoelectronic principle in hydrolytic reactions, the energy barrier for the breakdown of a tetrahedral intermediate relative to that for conformational change must be considered. This is essential in cases where the tetrahedral intermediate might undergo a conformational change prior to break down. As the energy barriers for the breakdown vary with ionic state, which is a function of pH, the various ionic states of tetrahedral intermediates must be taken into consideration.

TABLE 1 Predicted Cleavages of the Nine Conformers of Tetrahedral Intermediate 25 Shown in Fig. 2

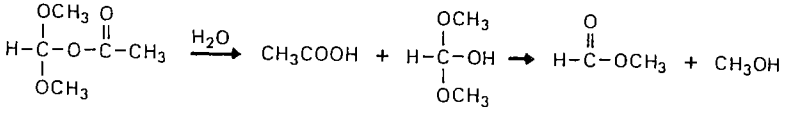
ester 26		conformer		ester 27
Z	⇌	A	⇏	
Z	⇌	B	⇌	E
Z	⇌	C	⇌	Z
	⇏	D	⇏	
	⇏	E	⇌	E
	⇏	F	⇌	Z
E	⇌	G	⇏	
E	⇌	H	⇌	E
E	⇌	I	⇌	Z

Hemi-orthoester intermediates have a weakly acidic hydrogen (from the O–H group), and they have electron pairs on the oxygen atoms which can be protonated in acidic medium. They can exist in three different ionic forms T^+, T°, and T^- depending on the acidity or the basicity of the medium. Since the pKa of a hemi-orthoester is about 10, it will exist in the T^+ and the T° forms in acidic medium and essentially in the T° form in neutral. In slightly basic medium (pH ≈8-10), it will exist in the T° and the T^- forms whereas in stronger basic medium (pH > 11), only T^- should be present.

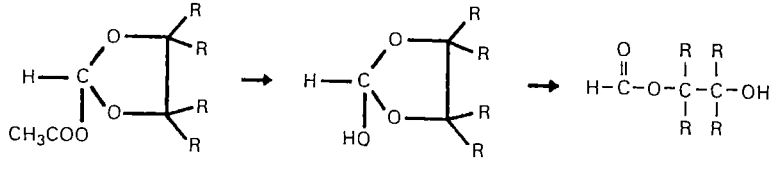


The energy barrier for conformational change of a given intermediate should not be influenced to a large extent by the ionic state, but the energy barrier for the cleavage should vary; it should be low for the T^+ and the T^- forms and high for the neutral form T°. This is in agreement with the evaluation of Guthrie (24) of the free energies for the formation and the cleavage of hemi-orthoesters in the acid-catalyzed, the uncatalyzed and the hydroxide-catalyzed hydrolysis of methyl formate and methyl acetate.

Capon and collaborators (25-27) have recently demonstrated that a neutral tetrahedral intermediate can exist in solution. The energy barrier for the cleavage of the T° form is consequently much higher than that for molecular rotation. They have observed that acetoxydimethoxymethane (28) in a mixture of acetone and water at -30°C gives acetic acid and the intermediate 29 which can easily be detected by nmr spectroscopy. Disappearance of the intermediate 29 was then observed to give the reaction products. Similar experiments were carried out with 2-acetoxy 1,3-dioxolan (30) and the tetramethyl derivative 31. With the latter, it was possible to obtain a solution in which more than 90% of the starting material was transformed into the intermediate 33. The hemi-orthoester 33 was much easier to detect than 32 because 33 breaks down at a slower rate than 32, and 31 hydrolyzes at a faster rate than 30. McClelland, Kresge, and their co-workers (28) have provided good evidence for the detection of some cyclic hemi-orthoesters in the hydrolysis of the corresponding orthoesters.



28 29



30 R = H
31 R = CH_3

32 R = H
33 R = CH_3

In acidic medium, the T° form should be present in equilibrium with the T^+ form because hemi-orthoesters are weak bases. Consequently, hemiorthoesters must be allowed to undergo molecular rotation prior to their breakdown in this medium. Also, there is no evidence so far that molecular rotation can compete with the breakdown of an intermediate in the T^+ ionic form. What we know is that the barrier for cleavage should be definitely lower in the T^+ than in the T° form (24). At pH higher than 11, hemiorthoesters will exist exclusively in the T^- ionic form, and it will be seen that in some cases, the energy barrier for the cleavage of T^- is lower than that of molecular rotation.

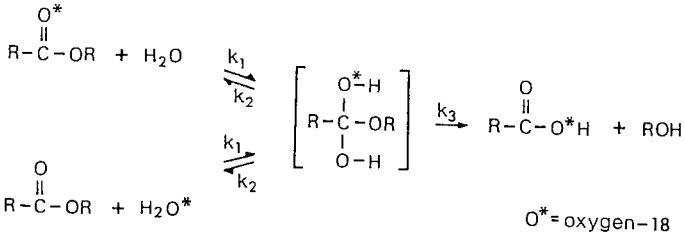
Now that the primary and secondary electronic effects have been explained, that the ionic state of tetrahedral intermediates in relation to the energy barrier for breakdown has been examined as well as the possibility that molecular rotation can compete with cleavage, experiments will be presented which show that there is stereoelectronic control in hydrolytic reactions. It should be pointed that it is not easy to find experiments to prove this theory because tetrahedral intermediates have extremely short life times and the knowledge of their stereochemistry cannot be obtained directly. The great advantage of the stereoelectronic theory is that it stresses the importance of the stereochemistry of tetrahedral intermediates, and at the same time, it shows that the orientation in space of the non-bonded electron pairs on heteroatoms is crucial to an understanding of the chemical reactivity of these species. Clearly, rigorous experimental evidence to prove this theory cannot be obtained by a single experiment.

Concurrent carbonyl-oxygen exchange and hydrolysis in esters

Concurrent carbonyl-oxygen exchange and hydrolysis have been demonstrated in the hydrolysis of esters by using oxygen-18 labeling. The oxygen exchange has been taken as experimental evidence for the formation of a tetrahedral intermediate in ester hydrolysis (29, 30). Bender and Heck (31) have also obtained evidence that the intermediate necessary for carbonyl-oxygen exchange lies on the reaction path of ester hydrolysis; both processes must therefore take place via the same tetrahedral intermediate.

Most substrates which have been studied show concurrent oxygen exchange, but there are exceptions. It has been postulated that reactions in which oxygen exchange is not detected still conform to the general mechanism;

in those cases oxygen exchange does not occur because the ratio of k_3/k_2 is greater than 100 (29, 30, 32-34). Although this explanation is certainly valid in some cases, a more complete rationalization can be obtained on the basis of the stereoelectronic theory.



Application of the principle of stereoelectronic control to the hydrolysis of esters under basic conditions leads to the following predictions: Z esters are allowed to undergo carbonyl-oxygen exchange but E esters cannot.

Reaction of an ^{18}O-labeled Z ester (34*) (Fig. 3) with hydroxide ion under stereoelectronic control should give the tetrahedral intermediate 35. Proton

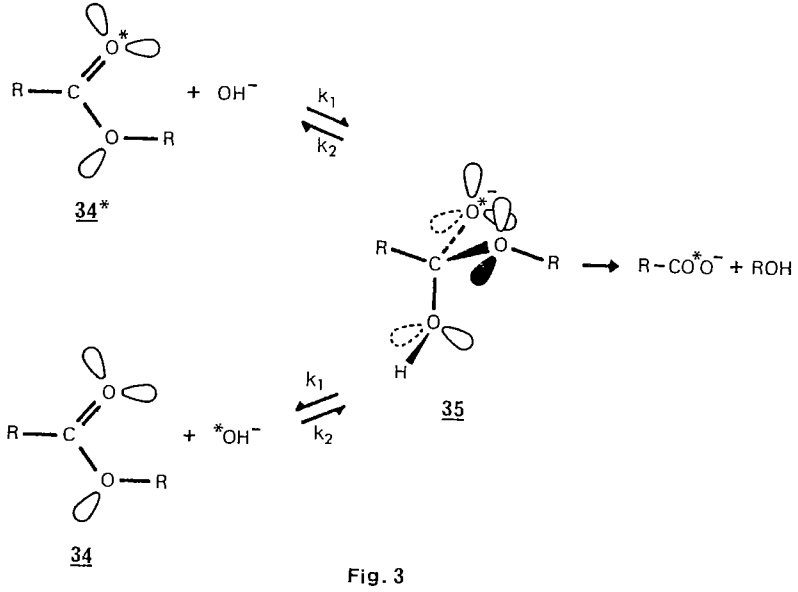


Fig. 3

transfer in the tetrahedral intermediate 35, assumed to be a very fast process (35), occurs before the cleavage of the tetrahedral intermediate; consequently, an O − H bond is considered equivalent to an electron pair.

It is easy to recognize a plane of symmetry in 35 if the hydrogen of the O − H group is replaced by an electron pair. Examination of the orientation of all the electron pairs in 35 shows that this intermediate can break down in three possible directions to give the starting labeled ester 34*, the products of the hydrolysis reaction, or the unlabeled ester 34 (after appropriate proton transfer). Consequently, the hydrolysis of Z esters should always occur with carbonyl-oxygen exchange with the solvent. The extent of exchange will depend on the relative values of k_3 and k_2. This is in agreement with experimental results described in the literature (31-34) for Z esters. It should however be pointed out that the fact that Z esters do undergo carbonyl-oxygen exchange is in accord, but does not constitute a proof for, the stereoelectronic theory.

The reaction of ^{18}O-labeled E ester (36*) (Fig. 4) with hydroxide ion should give the tetrahedral intermediate 37 which has the required orientation

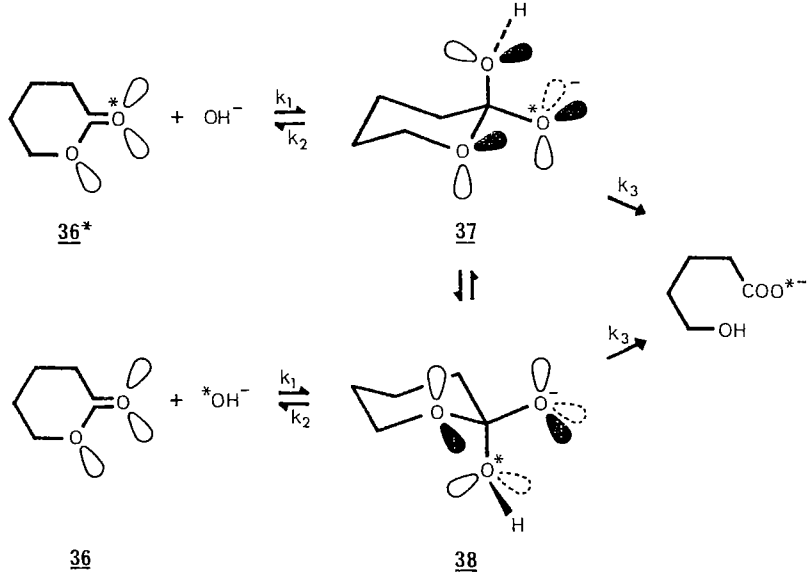
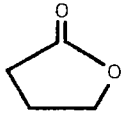


Fig. 4

of electron pairs to break down in two directions yielding either the starting labeled ester 36* or the hydrolysis product. Indeed, even after appropriate proton transfer, it is not possible to eject the equatorially oriented hydroxyl group ($-*O^- = -*OH$) in 37 because the ring oxygen does not have an electron pair properly oriented. The only manner by which the formation of unlabeled E ester 36 could occur is by a conformational change of 37 into the new conformer 38. If the barrier for conformational change 37 → 38 is too high and therefore this process cannot compete with the breakdown of 37, E esters should not undergo carbonyl-oxygen exchange concurrent with the basic hydrolysis.

It is also possible that the conformational change 37 → 38 does compete with the breakdown, and carbonyl-oxygen exchange still does not take place because k_3 would be much larger than k_2. The only scientific argument which has been advanced to rationalize that k_3 is always greater than k_2 is based on the secondary electronic effects (1, see also 39). Indeed, k_3 corresponds to the formation of a Z carboxylic acid (equivalent to a Z ester) while k_2 corresponds to the formation of an E ester, and as previously discussed, the secondary electronic effects predict that the formation of an E ester must involve more energy than that of a Z ester. Thus, even when conformational change is allowed, E esters should not undergo carbonyl-oxygen exchange. In accord with this prediction, γ-butyrolactone (39) (36), D-gluconolactone (40) (37) and isochromane-3-one (41) (38) do not undergo carbonyl-oxygen exchange during their basic hydrolysis.



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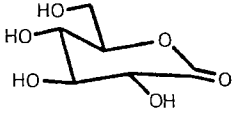

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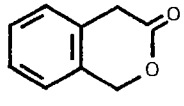
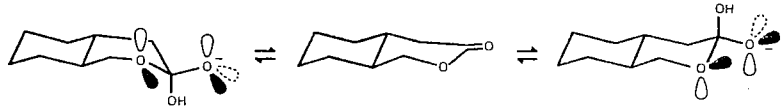


41

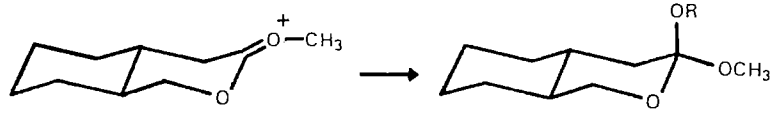
As a consequence of stereoelectronic control, it is possible to predict the direction of attack of a hydroxyl ion on a conformationally rigid lactone (40). For instance, we can consider the two possible modes of attack (α and β) of hydroxide ion on the bicyclic lactone 42. In both cases, the two oxygens of the lactone function must each develop an electron pair antiperiplanar to the new C—OH bond in the corresponding orthoacid. On that basis, a β-attack leads to the chair form 43 and an α-attack must give the less

stable boat form 44. Clearly, the energy difference between the two transition states leading to 43 and 44 must be more than 3 kcal/mol, and since these two modes of attack are competing, the reaction of hydroxide ion on the β face of 42 (axial attack) must be the favored process. Thus, stereoelectronic control provides not only an explanation for the non-exchange of the carbonyl-oxygen during the hydrolysis of lactones, it also predicts which face of a lactone function will react with hydroxide ion. Consequently, a more precise knowledge of the reaction mechanism can be obtained.



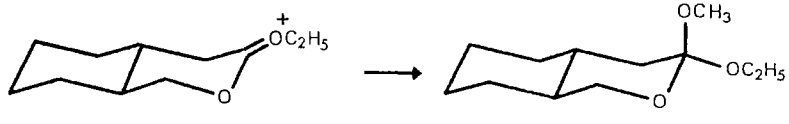
44 42 43

There is yet no direct experimental evidence which demonstrates that one particular face of a conformationally rigid lactone is more vulnerable than the other to a nucleophilic attack. However, rigorous evidence has been obtained from the study of the reactivity of the methyl and ethyl lactonium salts 45 and 46 with alkoxide ion (1, 3, 41). Indeed, the reaction of 45 with tetradeuterated methanol (CD_3OD), ethanol and chloro-2-ethanol gave specifically only the bicyclic orthoesters 47, 48, and 49 respectively. Similarly, the reaction of the ethyl lactonium ion 46 with methanol gave the bicyclic orthoester 50 exclusively, indicating again an exclusive β-attack (axial) by the alkoxide ion on the lactonium salt.



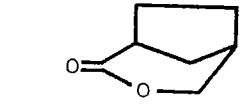
45

47 R = CD_3
48 R = C_2H_5
49 R = $ClCH_2CH_2$



46 50

Returning to lactones, it is interesting to compare the relative rates of hydrolysis in isomeric lactones such as 51 and 52 which are obtained from the Baeyer-Villiger oxidation of norbornanone (42). Attack by hydroxide ion should give the orthoacids 53 and 54 respectively. The orthoacid 54 has two 1,3-diaxial steric interactions between the axial OH group and the methylene groups of the bridge. Such interactions do not exist in orthoacid 53, so formation of 53 should demand less energy than that of 54. Indeed, the hydrolysis of a mixture of 51 and 52 was carried out (37) with sodium hydroxide and lactone 51 was found to hydrolyze at a much faster rate. This difference in the rate of hydrolysis has been used to separate mixtures of isomeric lactones (43-46).



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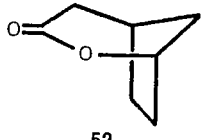

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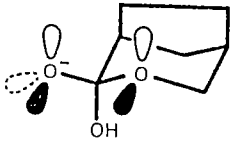

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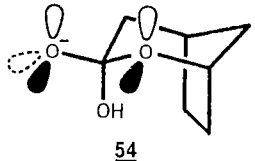
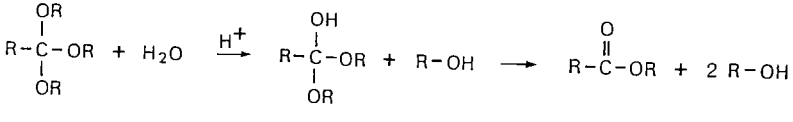


54

Hydrolysis of cyclic orthoesters

The formation of esters from the mild acid hydrolysis of orthoesters proceeds through the formation of a hemi-orthoester tetrahedral intermediate as described by the following equation (47-53).



hemi-orthoester

In a cyclic orthoester such as 55 (Fig. 5) when the two alkoxy groups are different, there is the possibility of forming three different hemi-orthoesters (56, 57, and 58) which can lead to three different esters, the two hydroxyesters 59 and 60 and the lactone 61. Thus, there is a possibility that some specific hemi-orthoesters will be generated which will lead to the preferential formation of one of the ester products. The mild acid hydrolysis of orthoesters is therefore a potential method to test the principle of stereoelectronic control in the formation and cleavage of hemi-orthoester tetrahedral intermediates.

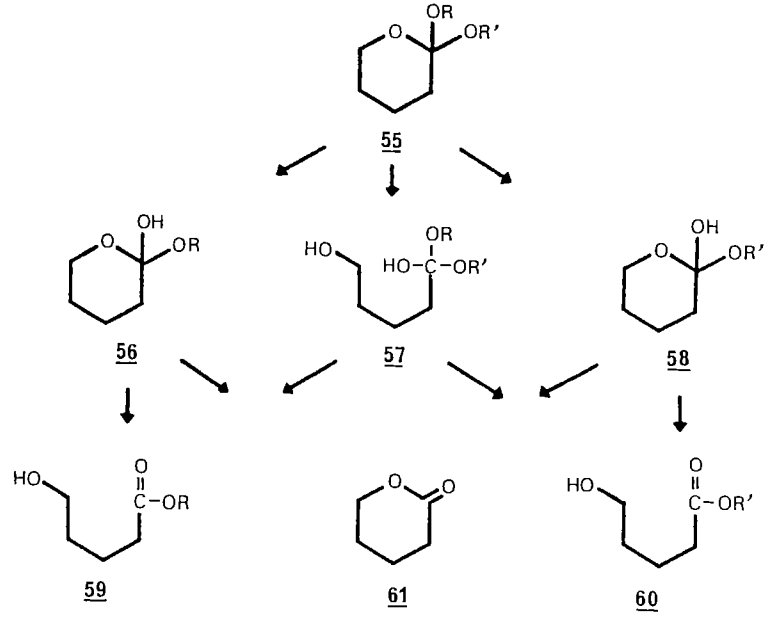


Fig. 5

A cyclic orthoester such as 55 in which the two alkoxy groups are identical will first be examined. There are nine gauche conformers which are theoretically possible for this type of cyclic orthoester and they are described in Fig. 6. The next task is to analyze each of these conformers on the basis of the principle of stereoelectronic control.

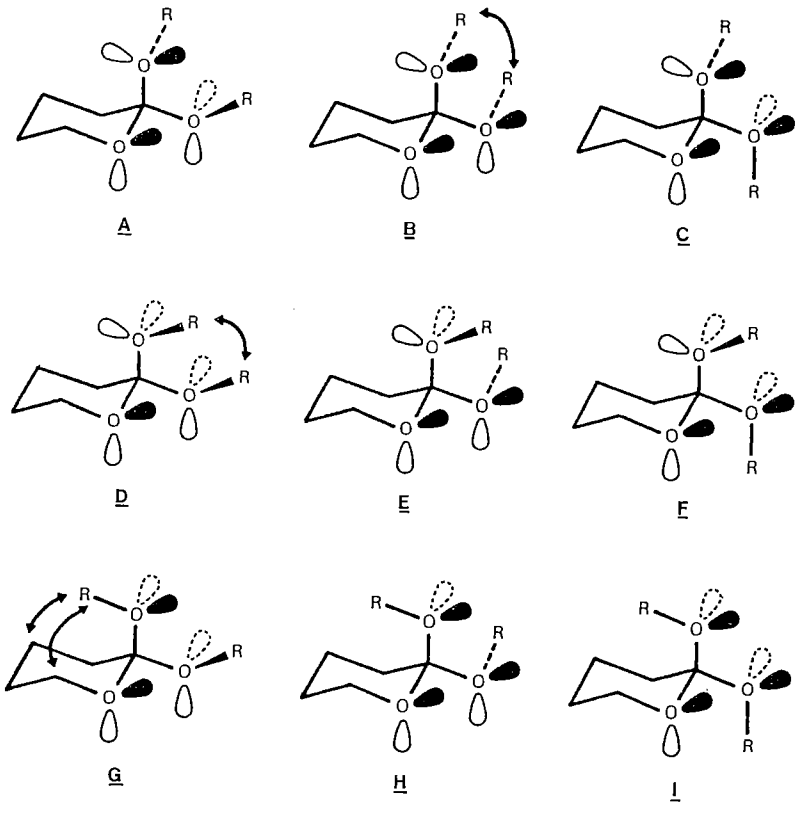
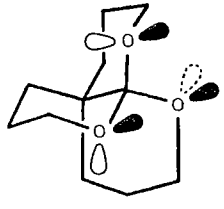


Fig. 6

The hydrolysis should proceed through the most energetically favored conformers which can expel one alkoxy group with the help of primary and secondary electronic effects after appropriate protonation. There is a severe steric interaction between the two R groups in conformers B and D; the population of these conformers at equilibrium will be very small. Conformers G, H, and I can also be ruled out by utilizing a similar argument; the R group of the axial alkoxy group has a severe steric interaction with the two methylene groups (C_3 and C_5) of the ring. The remaining four conformers A, C, E, and F do not have strong steric interactions and their cleavage can be analyzed by considering first the primary stereoelectronic effects (i.e.

an electron pair on each oxygen atom oriented antiperiplanar to the leaving group).

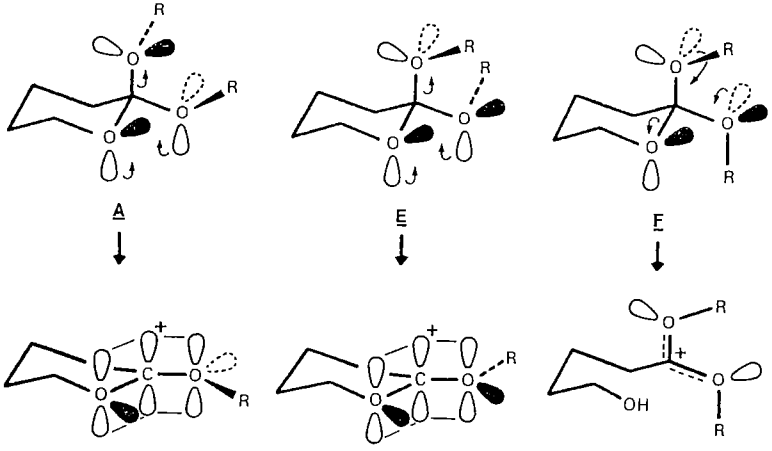
On that basis, conformers A and E can break down by the loss of the axial alkoxy group. Conformer F can undergo a cleavage via the fission of the carbon-oxygen bond of the ring but conformer C cannot break down (no primary electronic effect). Conformer C must therefore be unreactive and this prediction was verified experimentally (38, 50) by studying the reactivity of the tricyclic orthoester 62 (54-56) which is a perfect rigid model for conformer C, as shown by X-ray analysis (57). Indeed, compound 62 was found completely stable under the mild acid conditions that are normally used for the hydrolysis of other cyclic orthoesters. Thus, conformer C is a remarkably unreactive conformer which must be eliminated.



62

The reactivity of the three remaining conformers A, E, and F can now be analyzed by taking into account the secondary electronic effects. In the cleavage of the axial OR group in conformer A, the ring and the equatorial oxygens have each an electron pair oriented antiperiplanar to the leaving group (giving a primary electronic effect: $n\text{-}\sigma^* + n\text{-}\pi^*$). The equatorial oxygen has also an electron pair oriented antiperiplanar to the C – O bond of the ring oxygen; one secondary ($n\text{-}\sigma^*$) electronic effect will therefore help this cleavage which should yield the EZ lactonium ion 63. By comparison, conformer E can eject the axial alkoxy group with the help of the primary ($n\text{-}\sigma^* + n\text{-}\pi^*$) stereoelectronic effect only, and it will give the EE lactonium ion 64. Conformer F can undergo the cleavage of the C – O bond of the ring with the help of the primary stereoelectronic effect and of one secondary electronic effect yielding the EZ dialkoxycarbonium ion 65. Thus, on the basis of secondary electronic effects, cleavages of A and F are favored over that of conformer E. Finally, the cleavage of conformer F by comparison with that of conformer A must be a higher energy process because in the

reaction A → 63, there is formation of two molecules (63 and alcohol) and the ring is not broken whereas in the reaction F → 65, the ring is cleaved and only one molecule is formed. Thus, in the last process, the internal return (65 → F) might be important. The above analysis predicts that a cyclic orthoester should undergo hydrolysis via conformer A only.

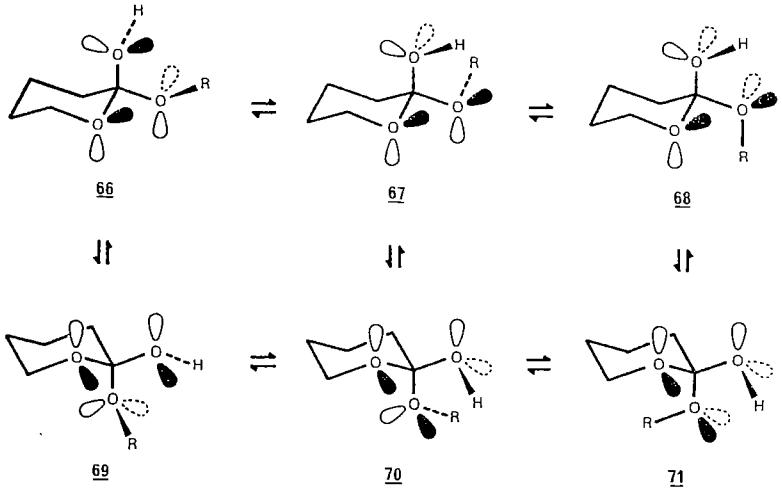


A E F

63 64 65

The next operation consists in the analysis of the hydration of lactonium ion 63 and the subsequent breakdown of the resulting hemi-orthoester. A stereoelectronically controlled attack of water on the lactonium ion 63 must take place on the β face yielding the tetrahedral conformer 66 (Fig. 7). As previously discussed for the case of lactones (cf. p. 70), a reaction with water on the α face of 63 would result in a tetrahedral intermediate having a boat conformation, and this process is therefore eliminated.

Under mild acidic conditions, tetrahedral intermediates exist in the T° and the T^{+} form and conformational change prior to the breakdown can take place (cf. p. 66). Thus, in systems where the tetrahydropyran ring cannot easily undergo a chair inversion, hydration of 63 will first give 66 which will then yield a mixture at equilibrium of rotamers 66, 67, and 68. In cases where the tetrahydropyran ring can easily undergo a chair inversion, there should be an equilibrium mixture of the six possible conformers 66-71. The relative population of 71 will be negligible because this conformer has a strong steric interaction between the R group and the ring. It should also



66 67 68

69 70 71

Fig. 7

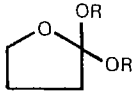
be pointed out that the exact orientation of the hydrogen atom of the OH group in the six conformers can be neglected because proton-exchange is a fast process.

By taking into consideration the primary and the secondary electronic effects, the predicted cleavages of the six conformers are the following. Conformer 67 cannot break down (no primary stereoelectronic control); it is therefore unreactive and must be eliminated. Conformer 66 can yield a hydroxy-ester having a Z conformation whereas conformer 68 can produce a hydroxy-ester which should have an E conformation. Interestingly, lactone formation from 66-68 cannot take place with primary stereoelectronic control. Thus, in cases where the tetrahydropyran ring is conformationally rigid, the hydrolysis must take place preferentially via conformer 66, yielding only the hydroxy-ester product in the Z conformation.

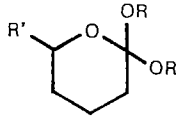
Intermediate 69 can either yield a Z (hydroxy-ester) or an E (lactone) ester. Intermediate 70 can only yield an E ester (lactone) whereas intermediate 71 can produce two E esters, the hydroxy-ester having an E conformation and the lactone. Thus, primary stereoelectronic effects allow the cleavage of intermediates 69-71 to produce either the hydroxy-ester or the lactone prod-

uct. However, the cleavage of 69 to yield a Z hydroxy-ester is favored by one secondary electronic effect. On that basis, it is predicted that only hydroxy-ester should be observed as hydrolysis product with conformationally labile cyclic orthoesters. On the other hand, it should also be pointed out that by comparison with the formation of lactone and alcohol, the formation of hydroxy-ester is not favored due to the reversibility of ring opening. If this factor is as important as one secondary electronic effect, lactone formation could compete with that of the hydroxy-ester. On that basis, a mixture of hydroxy-ester and lactone should be obtained with conformationally labile cyclic orthoesters.

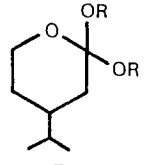
The first results reported (41) showed that the mild acid hydrolysis of the five cyclic orthoesters 72-76 (R=C_2H_5) gave the corresponding hydroxy-ester as the sole product of the reaction. It was found later by Capon and Grieve (58) that the hydrolysis of orthoester 73 (R=CH_3 or C_2H_5) gave a mixture of hydroxy-ester (≈70%) and lactone (30%). The hydrolysis of orthoesters 72-76 was subsequently repeated (59). It was confirmed that orthoester 73 indeed gave a ≈7:3 mixture of hydroxy-ester and lactone. A similar result was observed with orthoester 72 but the other three orthoesters 74-76 gave exclusively hydroxy-ester as previously reported.



72



73 R' = H
74 R' = CH_3



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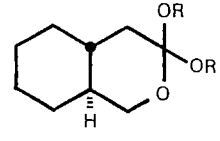
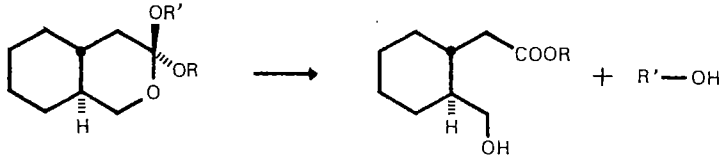


76

Compounds 74 and 75 cannot easily undergo a chair inversion because the methyl and the isopropyl groups of 74 and 75 would become axially oriented and would develop a strong 1,3-diaxial interaction with the axial alkoxy group. A similar situation would also occur in the corresponding hemi-orthoester intermediates; compounds 74 and 75 can therefore be considered equivalent to the conformationally rigid bicyclic orthoester 76. Consequently, the results obtained with compounds 74, 75, and 76 confirm the above conclusion that a conformationally rigid orthoester should give exclusively the hydroxy-ester product.

The results obtained with compounds 72 and 73 show that in orthoesters which are conformationally labile, the hydroxy-ester is still the major product but the formation of lactone can occur to some extent. Thus, it can be concluded that whenever a tetrahedral intermediate can exist as a mixture of conformers 66-71, the formation of an E ester (from 69, 70, or 71) will be able to compete (due to an entropy factor) to some extent with the formation of Z ester (from 66 or 69).

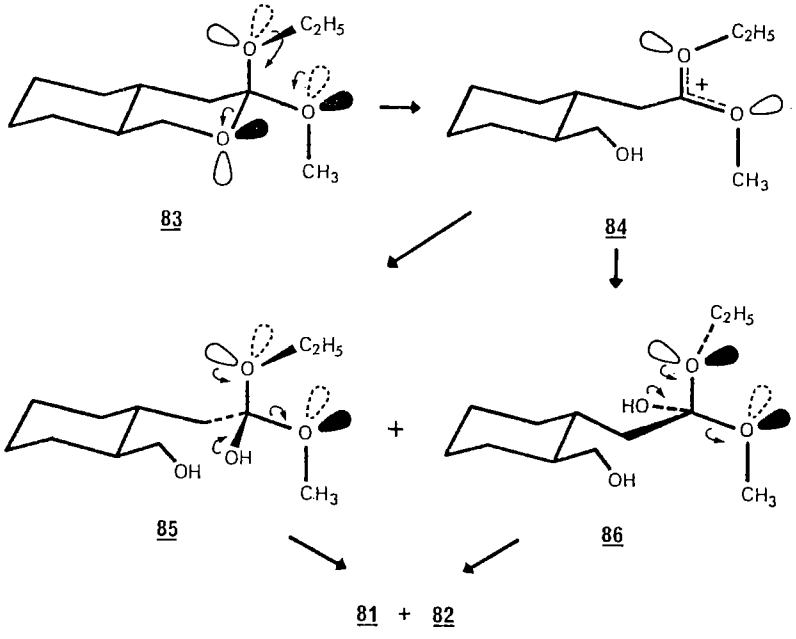
More precise information concerning the course of events in the acid hydrolysis of orthoesters was obtained from the study of the four bicyclic orthoesters 77-80 which have two different alkoxy groups. Each orthoester yielded exclusively the hydroxy-ester resulting from the ejection of the axial alkoxy group. Thus, 77, 78, and 79 afforded the same hydroxy methyl ester 81 whereas orthoester 80 furnished the hydroxyl ethyl ester 82. The reverse process which occurs under basic conditions, i.e. the addition of alkoxide ion to the corresponding bicyclic lactonium salt, has already been described (cf. p. 71) and it was shown to take place with the same specificity.



77 R' = CD_3, R = CH_3
78 R' = C_2H_5, R = CH_3
79 R' = $ClCH_2CH_2$, R = CH_3
80 R' = CH_3, R = C_2H_5

81 R = CH_3
82 R = C_2H_5

These results demonstrate that conformer F is definitely not involved in the course of the hydrolysis reaction. For example, if conformer F, i.e. 83 of orthoester 78 is examined on the basis of the stereoelectronic principle, it must yield a mixture of the two hydroxy-esters 81 and 82. Indeed, conformer 83 must produce first the open-chain dialkoxycarbonium ion 84 which after hydration would give the acyclic tetrahedral intermediates 85 and 86. Since internal rotation is allowed in 85 and 86, they would then give a series of different conformers which should fragment to give a mixture of the hydroxy-esters 81 and 82.

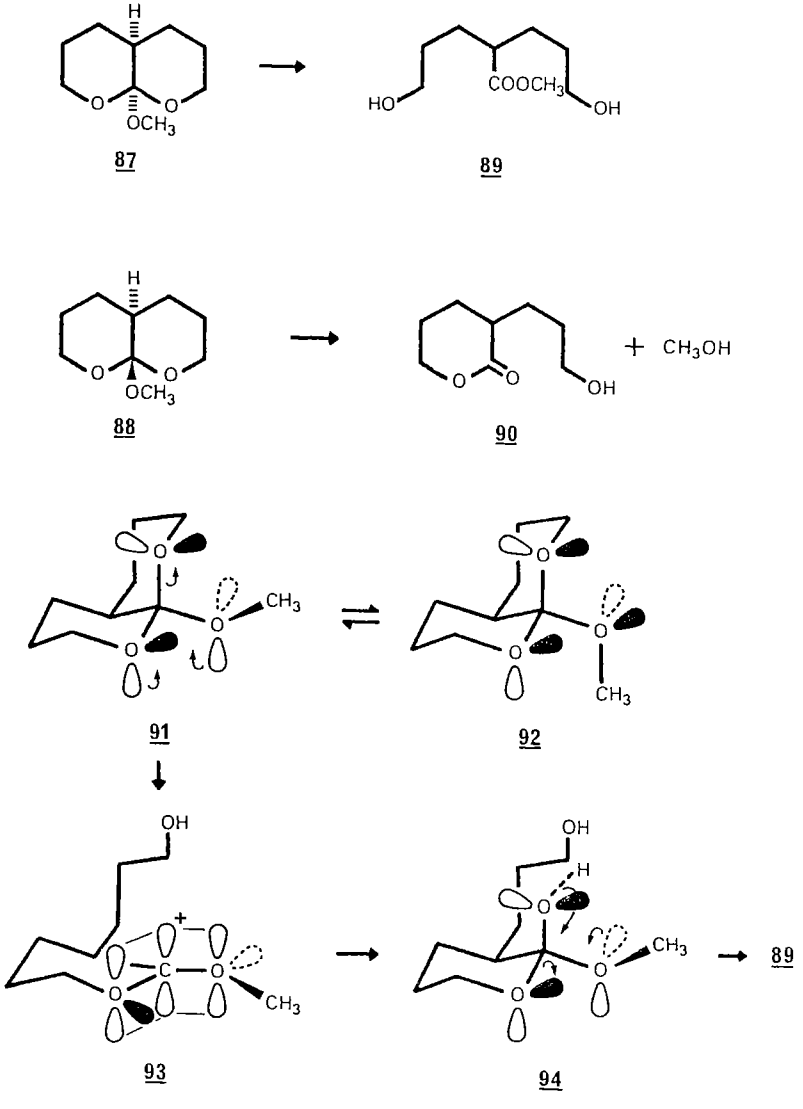


83 84 85 86

81 + 82

An interesting experimental result was observed in the study of the mild acid hydrolysis of the cis and the trans bicyclic orthoesters 87 and 88 (60). The cis orthoester 87 gave under kinetically controlled conditions the dihydroxy methyl ester 89 whereas the trans orthoester 88 produced directly the hydroxy-lactone 90 under the same experimental conditions. These results can be explained on the basis of the principle of stereoelectronic control.

The cis bicyclic orthoester 87 can exist in the two different conformations 91 and 92. The conformation 92 corresponds to that of the unreactive tricyclic orthoester 62, i.e. conformer C; it can therefore be eliminated. Conformer 91 can undergo the cleavage of the axial C–O bond with stereoelectronic control to produce the lactonium ion 93 which after hydration will give the hemi-orthoester 94. Since the chair inversion in 94 is not favored because the hydroxyalkyl side chain would have to take the axial orientation, it is expected that 94 would give the dihydroxy methyl ester 89 preferentially.



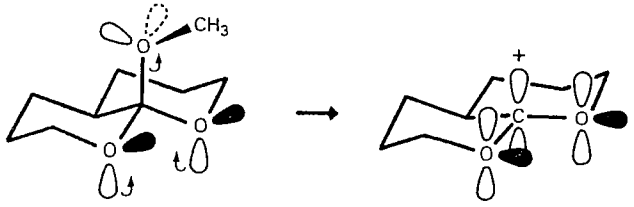
87 89

88 90

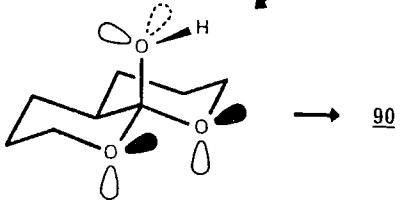
91 92

93 94

The trans bicyclic orthoester 88 must exist in the conformation 95 and the primary stereoelectronic effects permit the ejection of the methoxy group only, yielding the bicyclic lactonium ion 96 which after hydration (→97) and cleavage will give the hydroxy-lactone 90 only. The process 97 → 90 cannot occur with stereoelectronic control; its energy barrier must therefore be higher than in other cases. Kaloustian and Khouri (61) have shown that the reaction of sodium methoxide with the bicyclic salt 96 gave the trans orthoester 95 specifically.



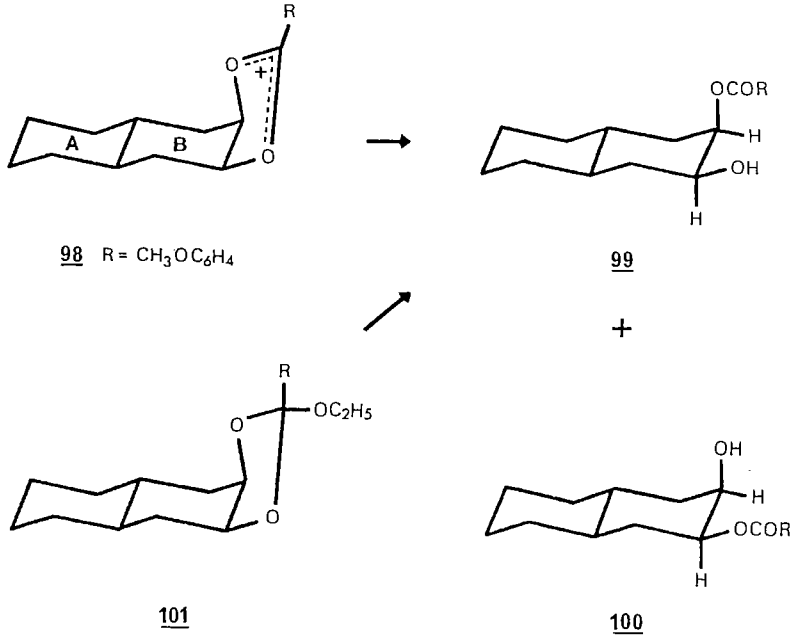
95 96



97 90

King and Allbutt (60, 62) have described the stereoselective hydrolysis of the dioxolenium ion 98 derived from a trans-decalin. Mild acid hydrolysis of 98 afforded almost entirely the axial ester product 99 with only a trace (<0.5%) of the equatorial ester 100. A similar result was obtained by using mild basic conditions. The authors further established by equilibration studies that the equatorial ester 100 is the most stable isomer, demonstrating that the formation of the axial isomer 99 is subject to kinetic rather than thermodynamic control. Essentially identical results were produced with two other dioxolenium salts derived from steroids.

The same authors have also carried out the hydrolysis of orthoesters 101. When R=CH_3, C_2H_5 or C_6H_5, they found again an almost exclusive formation of



98 R = $CH_3OC_6H_4$ 99 + 100 101

the axial ester 99 in preference to the equatorial ester 100. When R=H, they obtained a mixture of 60% axial ester and 40% equatorial ester under kinetically controlled conditions. The orthoester 101 (R=CH_3, C_2H_5 or C_6H_5) yielded the same result as the dioxolenium salt 98, and this is not surprising as 98 is believed to be an intermediate in the hydrolysis of 101. Other workers have also observed the formation of axial esters in preference to equatorial esters (63-66).

King and Allbutt have explained their results by invoking either a preferential protonation of the equatorial oxygen in the corresponding hemiorthoester (60, 62) or a combination of steric and stereoelectronic factors (60). It is highly probable that both explanations are valid because the greater ease of protonation of the equatorial oxygen is a direct consequence of the stereoelectronic effects (which make that oxygen atom more basic (cf. p. 31)). It should be further pointed out that these workers were the first to report that stereoelectronic effects might play a role in hydrolysis

reactions. However, the generality and the importance of the principle of stereoelectronic control was not fully recognized.

According to the present theory, these reactions can be explained in the following manner. Since dioxolenium ions are essentially planar (8, 9), the chair form of ring B of salt 98 must be distorted towards a half-chair. Hydration of 98 with stereoelectronic control must take place from the α face to give the half-chair hemi-orthoester 102 (Fig. 8), because the steric hindrance between the incoming water molecule and ring B must inhibit

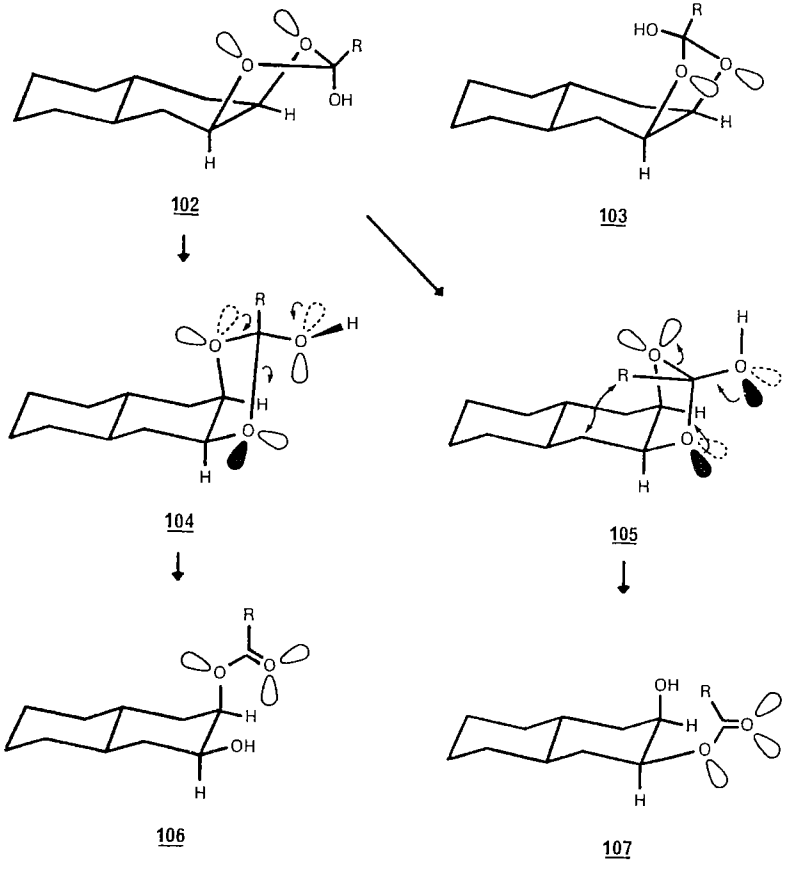


Fig. 8

the formation of hemi-orthoester 103. Once the hemi-orthoester 102 is formed, it can then take the conformations 104 or 105 where the tension caused by the half-chair of ring B is released. Conformers 104 and 105 can break down with the help of the primary stereoelectronic effects to give the axial ester 99 and the equatorial ester 100 respectively.

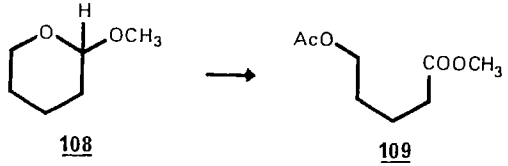
The R group in 105 is in a 1,3-diaxial arrangement with a methylene group of ring B (cf. arrow); thus when R is a large group, conformer 104 will be favored over 105, and the axial ester will be preferentially formed. However, when R is a hydrogen atom, 104 and 105 will exist as an equilibrium mixture and a mixture of axial and equatorial esters 99 and 100 will be formed. This is essentially the steric and stereoelectronic argument used by King and Allbutt (62). There is an additional reason for the preferential formation of axial ester which is simply that the cleavage of 104 gives an axial ester where the ester function will be produced in the Z conformation 106 whereas the cleavage of 105 will form an equatorial ester 107 which has the less stable E conformation.

Ozonolysis of tetrahydropyranyl ethers

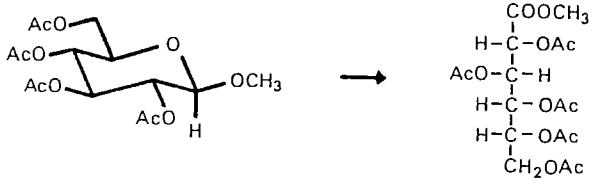
The relationship between the conformation of the acetal function and its reactivity towards ozone has been described in detail (cf. p. 41). It was shown that the insertion of ozone into the C—H bond of the acetal function to form the corresponding hydrotrioxide tetrahedral intermediate is subject to stereoelectronic control. This section deals with the next step of this reaction, i.e., the decomposition of the hydrotrioxide tetrahedral intermediate to yield the ester product. Experimental results will be presented to show that this step is also controlled by stereoelectronic effects. These results can therefore be used as evidence for the principle of stereoelectronic control in ester formation.

In the course of the studies on the ozonolysis of acetals (67-69), it was observed that the reaction of ozone with simple tetrahydropyranyl ethers as well as with conformationally rigid β-glycosides always gave the corresponding hydroxy-esters exclusively, under kinetically controlled conditions, lactone formation was never observed. For example, ozonolysis of 2-alkoxytetrahydropyran 108 under acetylating conditions (O_3 in Ac_2O-AcONa) gave alkyl 5-O-acetyl pentanoate 109 exclusively. Similarly, oxidation, of methyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside 110 yielded the corre-

sponding penta-O-acetyl aldonic acid methyl ester 111. Similar results were obtained with tetrahydrofuranyl ethers. Ozonolysis of 2-methoxytetrahydrofuran (112) gave only methyl-4 O-acetyl-butanoate (113); the corresponding γ-butyrolactone was not detected. Likewise, methyl 2,3,5-tri-O-acetyl α and β-D-ribofuranoside (114 and 115) were both converted into methyl 2,3,4,5-tetra-O-acetyl-D-ribonate (116).



108 109



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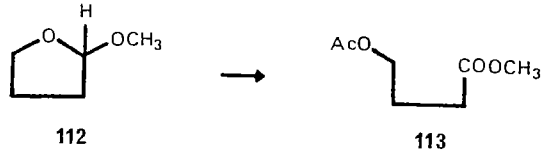
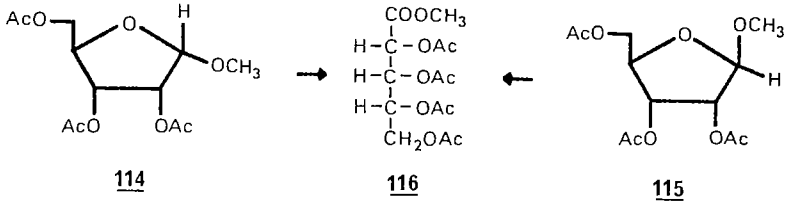
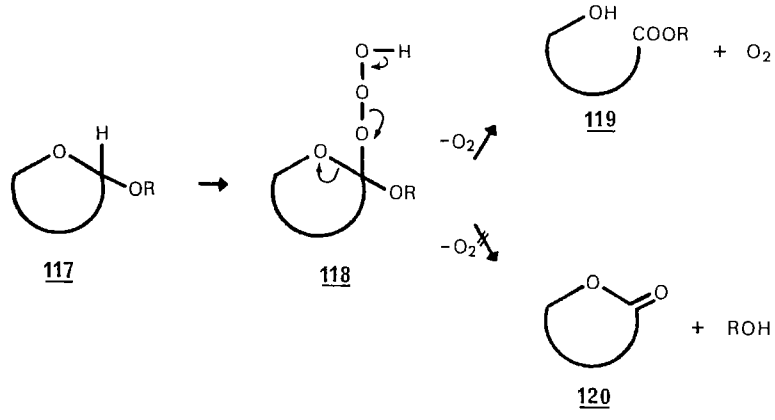


112 113



114 116 115

These results demonstrate that the hydrotrioxide intermediate 118 which is formed from a cyclic acetal such as 117 is cleaved in a completely specific manner, yielding the hydroxy-ester 119 in preference to the lactone 120.



117 118 119 120

These results are very similar to those obtained from the mild acid hydrolysis of the cyclic orthoesters described in the preceding section. The difference is that in the ozonolysis reaction, the tetrahedral intermediate which is formed bears a hydrotrioxide group instead of a hydroxyl group. Also the fragmentation must take place on the T° neutral form of the hydrotrioxide intermediate (70), and it is likely that the hydroxyl group forms a hydrogen bond with the ring oxygen in order to assist its departure, forming molecular oxygen and the hydroxy-ester (119). Except for these differences, the fragmentation of the hydrotrioxide intermediate remains essentially the same as that for the hemi-orthoester intermediate, and must therefore be governed by the same electronic factors.

Consequently, with conformationally rigid tetrahydropyranyl ethers which have an alkoxy group in the equatorial configuration (as in β-glycosides), or with conformationally mobile compounds, the reaction of ozone must take place with either conformer 121 or conformer 122 (Fig. 9). The resulting hydrotrioxides are 124, 125, and 126 when the tetrahydropyran ring is rigid, and an equilibrium mixture of the six conformers 124-129 when that ring can easily undergo a chair inversion. The $HO_2 - O$ bond of the hydrotrioxide intermediate will be cleaved during the formation of the ester function;

that bond is therefore equivalent to an electron pair and its precise orientation in space does not need to be considered now.

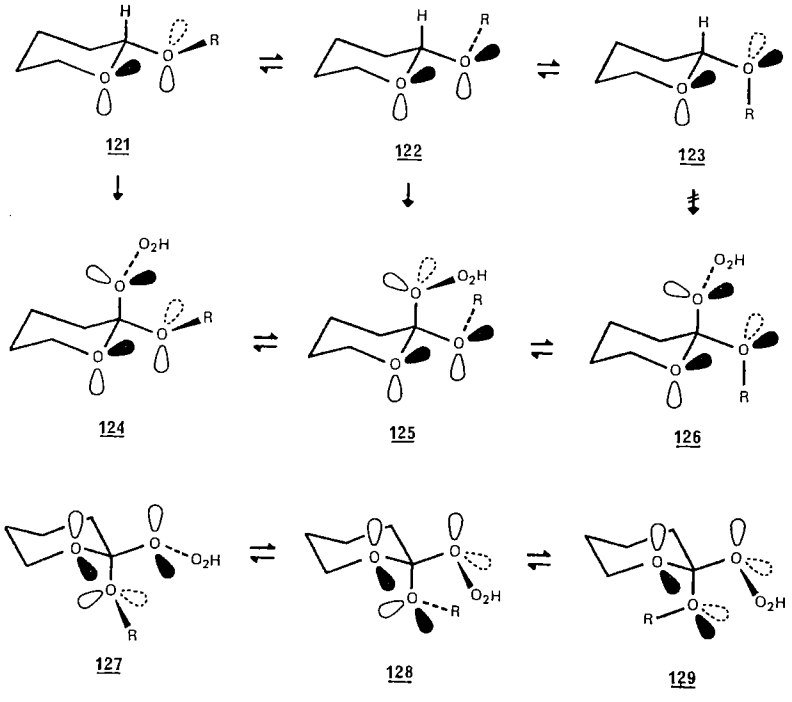
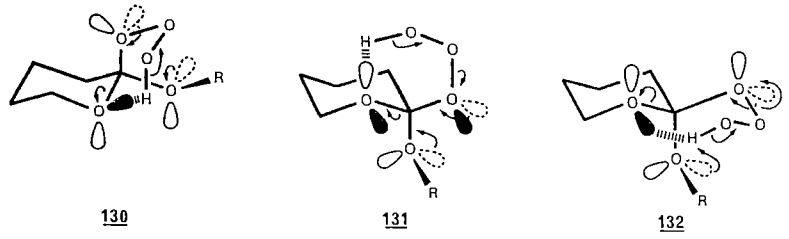
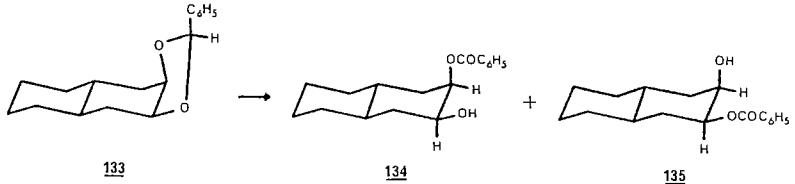


Fig. 9

We have discussed (cf. p. 77) the preferred cleavages of the six hemiorthoester conformations corresponding to the hydrotrioxide intermediates 124-129. It is not necessary to repeat this discussion here, except to mention that, on this basis, only conformers 124 and 127 can be cleaved with primary and secondary stereoelectronic control to produce the hydroxy-ester with the ester function in a Z conformation. Thus, when the tetrahydropyran ring is locked conformationally, fragmentation must take place from intermediate 124 and if this ring is mobile, the cleavage will occur from either 124 or 127. If it is a requisite that the hydroxyl group must form a hydrogen bond with the leaving group (70), then the true intermediate for the fragmentation of 124 would correspond to 130 whereas that of 127 would be either 131 or 132.

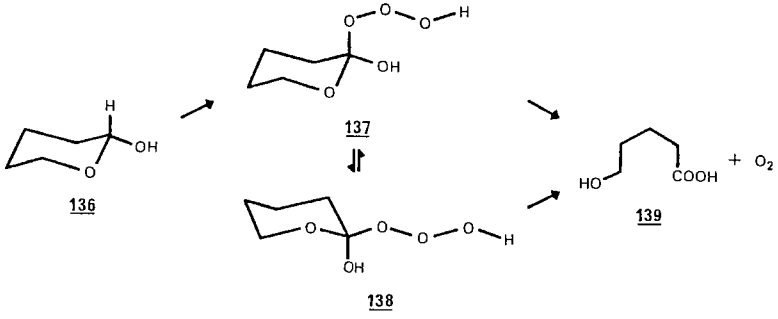


Ozone oxidation of the trans-decalin diol benzylidene 133 has been carried out (71). Under kinetically controlled conditions, it produces the axial benzoate 134 in preference to the more stable equatorial benzoate 135. Similar results were obtained with an analogous case derived from cholestane-2β,3β-diol. These results are essentially identical to those obtained by King and Allbutt (60, 62) in their study on the hydrolysis of dioxolane orthoesters and dioxolenium salts (cf. p. 82), and can therefore be explained in the same manner. These results further confirm that the oxidation of acetals by ozone produces an intermediate which behaves like the hemiorthoester tetrahedral intermediate which is formed in the hydrolysis of orthoesters.



The ozonolysis of tetrahydropyranyl alcohol was also carried out (72) and it proceeds smoothly to give the hydroxy-acid in essentially quantitative yield. This compound 136 must give intermediate 137 and then a mixture of 137 and 138, which fragment to give the hydroxy-acid 139 (a Z carboxylic acid) instead of δ-valerolactone. This result further demonstrates that k_3 must be larger than k_2 in the case of tetrahedral intermediates derived from lactones, a conclusion which was reached previously in the study of the carbonyl-oxygen exchange during the hydrolysis of lactones (cf. p. 70).

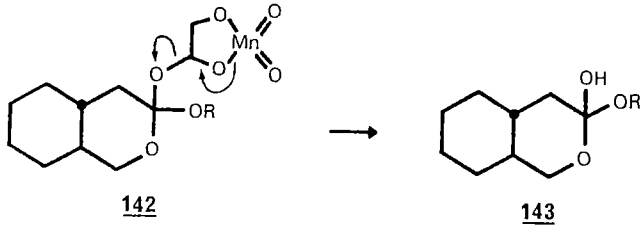
It is appropriate to point out here that the development of the theory of stereoelectronic control has had its origin in the study of the ozonolysis of the acetal function (67, 68). It was first demonstrated that there



is a direct relationship between the orientation of the electron pairs relative to the C — H bond and the reactivity of the acetal function toward ozone. As a second step, it was postulated that this reaction proceeds via the formation of a hydrotrioxide tetrahedral intermediate. As a third step, it remained to explain the specific decomposition of such an intermediate to a hydroxy-ester. This led to the postulate that the orientation of the electron pairs, which plays a key role in the reaction of ozone with the C — H bond of the acetal function, might also play an equivalent role in the cleavage of these tetrahedral intermediates. Finally, as it was realized that the hydrotrioxide intermediate 118 is equivalent to a hemi-orthoester, the tetrahedral intermediate normally observed in ester hydrolysis, the importance of the principle of stereoelectronic control in hydrolytic reactions was then fully recognized.

Cleavage of vinyl orthoesters

The study of the cleavage of the axial and the equatorial vinyl bicyclic orthoesters 140 and 141 (Fig. 10) with potassium permanganate was reported recently (1, 3). Permanganate reacts with the vinyl orthoester double-bond yielding first 142 and then the tetrahedral intermediate 143. On that basis,



140 must produce the tetrahedral intermediate 144 with an axial OH group whereas 141 must give 145 with an equatorial OH group. Consequently, the configuration of the tetrahedral intermediate is determined only by that of the vinyl orthoester from which it originates.

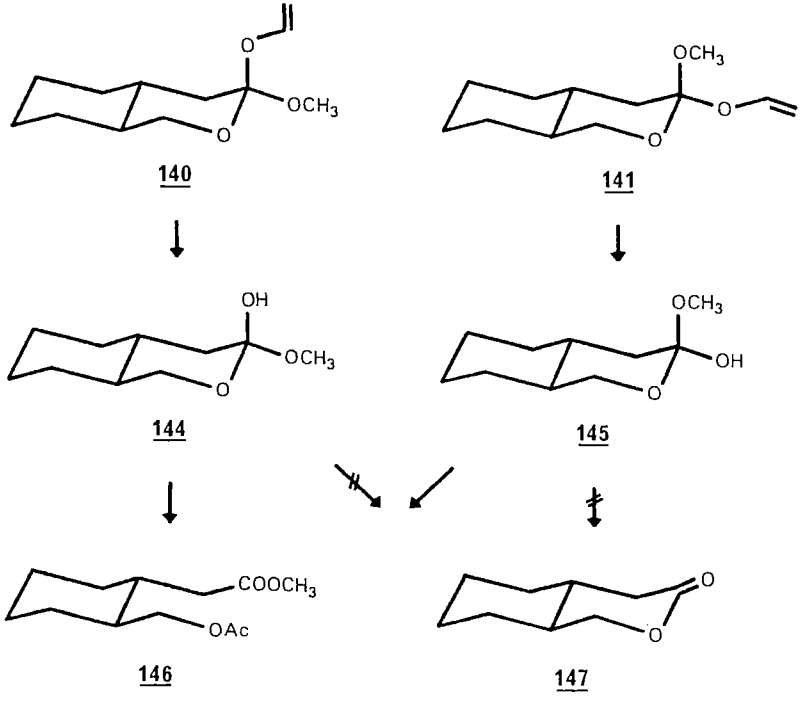


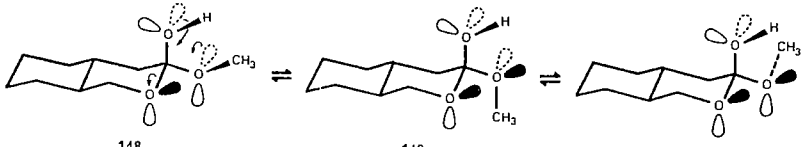
Fig. 10

In previous studies, i.e. concurrent carbonyl-oxygen exchange in the hydrolysis of esters, acid hydrolysis of orthoesters and oxidation of acetals by ozone, the configuration of the tetrahedral intermediate was determined by the application of the principle of stereoelectronic control. There could be some ambiguity in these experiments as the theory of stereoelectronic control is used to predict both the stereochemistry of the tetrahedral intermediate as well as its breakdown. The oxidation cleavage of vinyl orthoesters can therefore be considered a more powerful experimental technique in that respect because the configuration of the hemi-orthoester

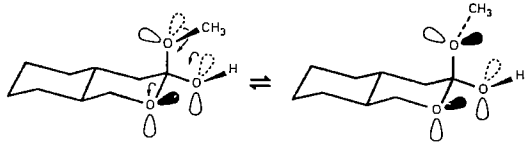
is determined independently of the stereoelectronic theory. It has also the advantage that the behavior of a tetrahedral intermediate having either an axial or an equatorial hydroxyl group can be observed in separate experiments.

The permanganate oxidation of axial and equatorial vinyl orthoesters 140 and 141 was carried out in a buffered solution (pH = 10) mixed with acetonitrile. The reaction mixture was then esterified with acetic anhydride and pyridine. Both vinyl orthoesters gave an identical result: >95% of acetoxy ester 146 and <5% of bicyclic lactone 147.

These results can again be explained on the basis of the stereoelectronic theory. Compound 140 must give a mixture of conformers 148, 149, and 150. We have previously discussed (cf. p. 77) that none of these conformers can break down with primary stereoelectronic control to give the lactone, and that only conformer 148 can yield the hydroxy-ester in the Z conformation. Thus, the formation of hydroxy-ester from 140 must come from the cleavage of 148. The equatorial vinyl orthoester 141 must produce a mixture of conformers 151 and 152. It has also been previously discussed that stereoelectronic effects predict that conformer 151 can either give a Z (hydroxy-ester) or an E (lactone) ester whereas conformer 152 can only give the lactone product. Since the hydroxy-ester is the product of the reaction, this result demonstrates again the importance of the secondary stereoelectronic effects which predict that a Z ester will be formed preferentially to an E ester. Thus formation of hydroxy-ester from 141 must come from the cleavage of 151.



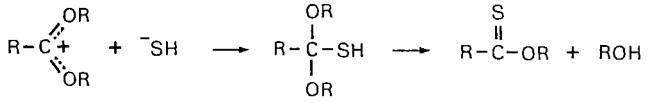
148 149 150



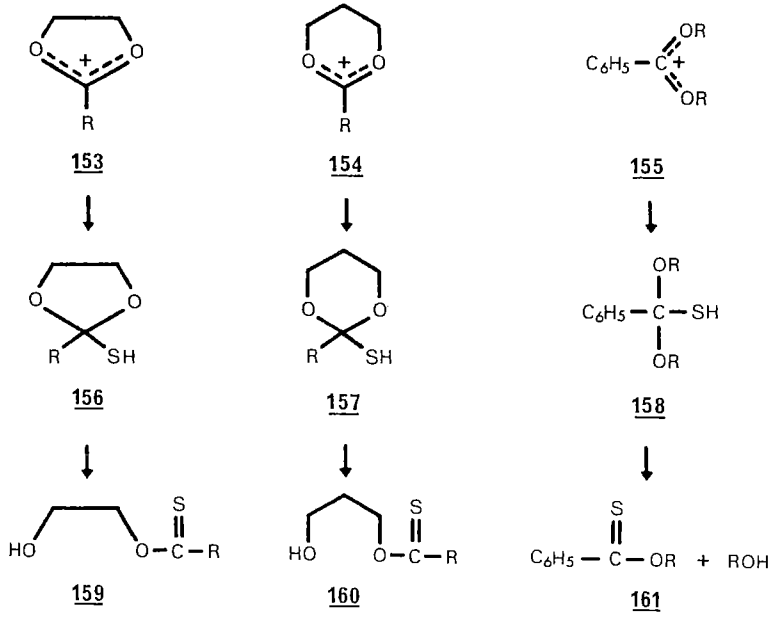
151 152

Cleavage of tetrahedral intermediates containing a sulfur atom

Kaloustian and Khouri (73-76) have studied the cleavage of hemi-orthothiol ester tetrahedral intermediates generated by the reaction of dialkoxycarbonium ions with hydrosulfide anion in aprotic solvent. The results obtained show that cleavage of the hemi-orthothiol ester intermediate is subject to stereoelectronic control.



The authors (73) have first observed that cyclic dialkoxycarbonium ions 153 and 154 (R=CH_3 or C_6H_5) as well as acyclic dialkoxycarbonium ion 155 (R=CH_3 or C_2H_5) reacted with sodium hydrosulfide (NaSH) to give monothioesters 159 and 160 and thionobenzoate 161 respectively. These results show that the hemi-orthothiol esters 156, 157, 158 must be formed as intermediates in these reactions. The salts 153 and 154 (R=H) behave in a similar fashion (nmr and tlc analyses), but isolation of the products (159 and 160, (R=H)) was thwarted by their high reactivity.

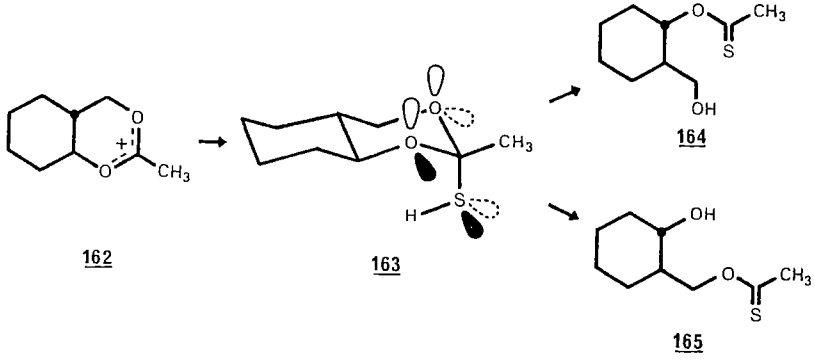


153 154 155

156 157 158

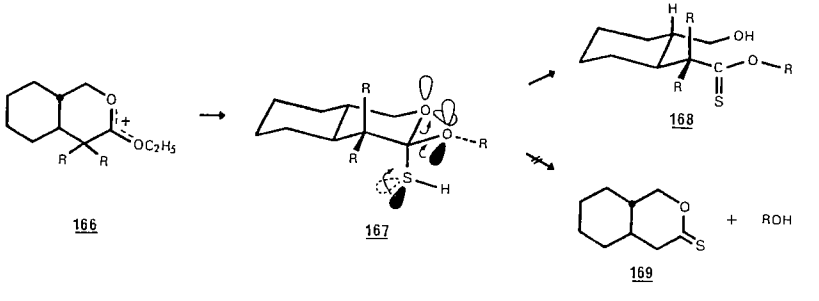
159 160 161

Secondly, it was observed by the same authors (61) that the reaction of bicyclic 1,3-dioxolenium salt 162 with sodium hydrosulfide gave a mixture of the two isomeric hydroxy thionoacetates 164 and 165 in a 1.5:1 ratio.



162 163 164 165

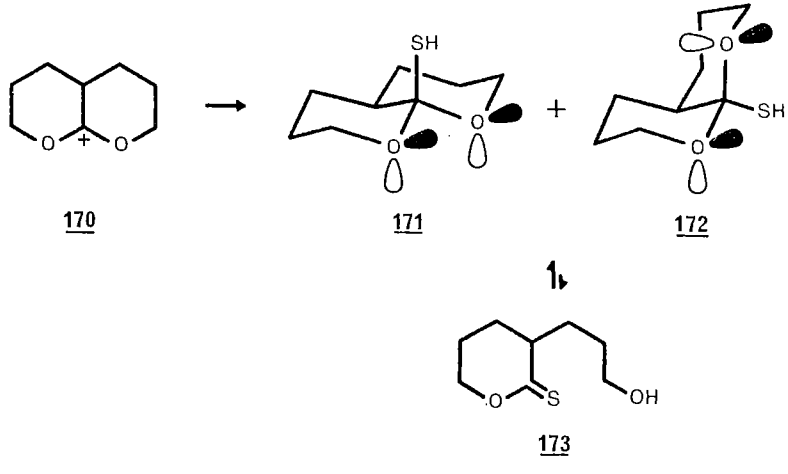
On the other hand, the same reaction with the bicyclic lactonium salt 166 (R=H or CH_3) yielded the hydroxy thionoester 168 exclusively; the other a priori possible product, i.e. the thionolactone 169, was not produced. Following the principle of stereoelectronic control, the salt 162 must react with sodium hydrosulfide to give the axial hemi-orthothiol ester 163. The specific formation of methyl orthothio ester 163 (SH=SCH_3) from the reaction of ion 162 with methyllithium mercaptide (CH_3SLi) confirmed the configuration of 163. The intermediate 163 can break down with stereoelectronic control to yield the two hydroxy thionoesters 164 and 165. The reaction of ion 166 with sodium hydrosulfide must produce the intermediate 167 which can only break down to yield the hydroxy thionoester 168 because the cleavage of 167 to furnish the thionolactone 169 cannot take place with stereo-



166 167 168 169

electronic control. This rationalization of Kaloustian and Khouri based on the principle of stereoelectronic control is completely consistent with their experimental results.

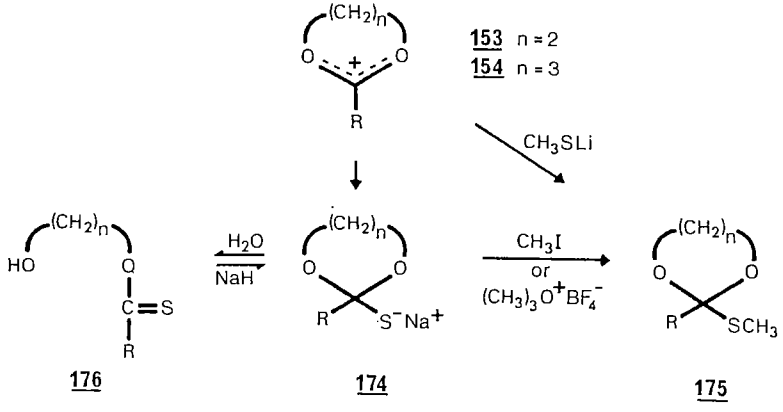
The same workers (61) have also studied the reaction of bicyclic salt 170 with sodium hydrosulfide. To their surprise, they isolated a mixture of hemi-orthothiol esters 171 and 172 in preference to the hydroxy thionolactone 173. They further showed that 171 and 172 are rapidly interconverted. The reluctance of 172 to give hydroxy thionolactone 173, despite stereoelectronic assistance, could be explained on kinetic and/or thermodynamic grounds. Kaloustian and Khouri favored the kinetic explanation because other hydroxythionoesters do not exist in the tetrahedral form. This writer favors the thermodynamic explanation. Compound 173 has a thionolactone rather than a thionoester functional group. It is possible that, as in the case of lactones by comparison with esters, thionolactones might be more reactive than thionoesters, and on that basis, the equilibrium would be in favor of 171 and 172 in preference to 173. The interconversion 171⇌172 cannot occur with stereoelectronic control unless considerable twisting of one of the rings in 171 can take place. The interconversion 171⇌172 must therefore have a relatively high energy barrier.



170 171 172 173

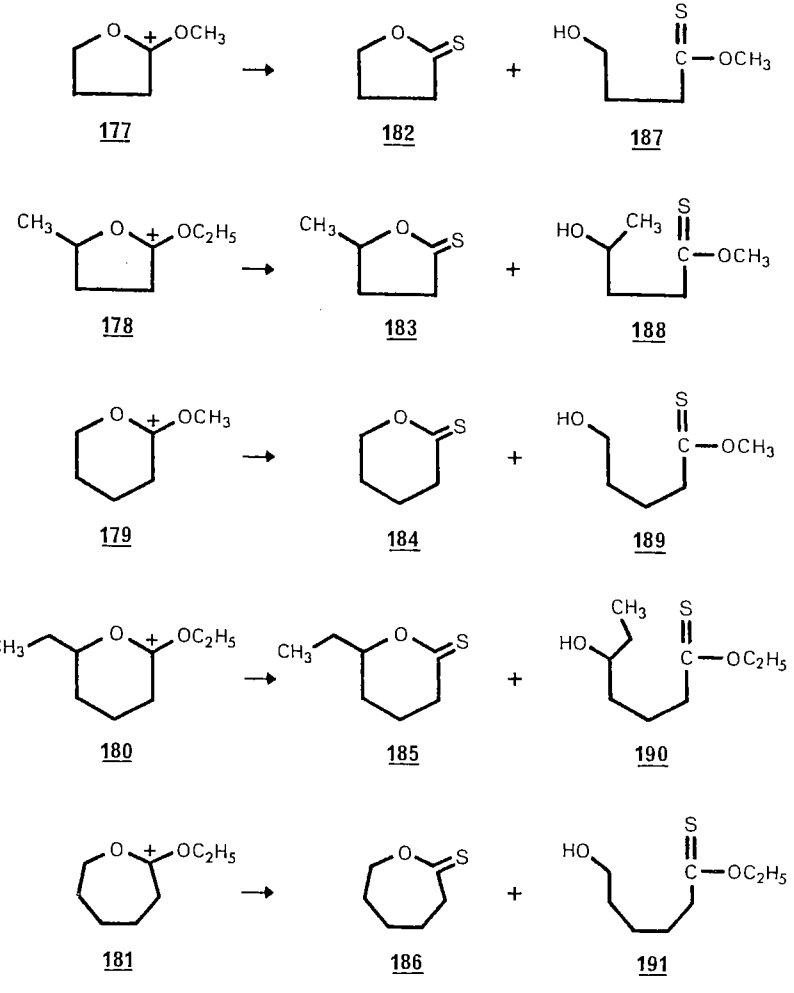
Kaloustian and Khouri (74) have also observed that the sodium salts 174 (n=2 and 3) of the hemi-orthothiol esters 156 and 157 are stable tetrahedral intermediates. These insoluble salts were produced by reacting the

dialkoxycarbonium ions 153 and 154 with sodium sulfide (Na_2S). These stable insoluble tetrahedral species were fully characterized by the following chemical interconversions. Reaction of 174 with methyl iodide or trimethyl oxonium tetrafluoroborate gave the cyclic methyl orthothioesters 175 (n=2 and 3) which were also produced from the reaction of methyllithium mercaptide (CH_3SLi) with the cyclic dialkoxycarbonium ions 153 and 154. Treatment of hemi-orthothiolate ester anions 174 (n=2 and 3) with water gave the hydroxy thionoesters 176 (n=2 and 3). Finally, treatment of hydroxy thionoester 176 (n=2 and 3) with sodium hydride in acetonitrile regenerated the tetrahedral salts 174 (n=2 and 3). These results show clearly that sulfur containing tetrahedral intermediate sodium salts 174 are more stable than the corresponding thionoester sodium alcoholates (176, $OH{=}O^-Na^+$).



Finally, the reaction of lactonium ions 177-181 with sodium hydrosulfide in acetonitrile at 0°C was also studied (75, 76). Each ion gave a mixture of the corresponding thionolactones 182-186 and hydroxy thionoesters 187-191. With the exception of 191, hydroxy thionoesters 187-190 underwent on mild acid catalysis some degree of lactonization which was then followed by rapid decomposition. These results suggest that 187-191 are primary products resulting directly from the breakdown of the corresponding tetrahedral intermediate. They further indicate that the formation of thionolactone could compete with the formation of hydroxy thionoesters. However, temperature studies of the sulfhydrolysis of salt 180 revealed that the cleavage products 185 and 190 were formed in the ratio of 0:100 at -78°C,

20:80 at -42°C and 47:53 at 0°C. Thus, at low temperature, the cleavage of the hemi-orthothiol ester derived from 180 occurs by preferential cleavage of the endocyclic C — O bond. The breakdown of this intermediate would therefore take place with stereoelectronic control as in the case of conformationally rigid hemi-orthothiol ester 167.



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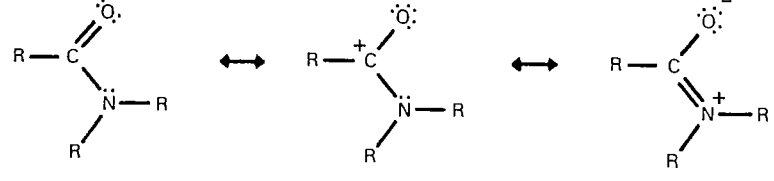
CHAPTER 4

AMIDES AND RELATED FUNCTIONS

Stereoelectronic effects and the amide function

This Chapter deals with the stereoelectronic effects which control the cleavage of tetrahedral intermediates during the formation or the hydrolysis of the amide function (1-4). These electronic effects will be examined in the amide function first.

In amides, the nitrogen electron pair is n-π conjugated with the carbonyl group and this electronic delocalization is normally expressed by resonance structures 1, 2, and 3. As a result, the amide function is essentially planar and it is assumed that the three atoms (C, N, and O) of this function are sp^2 hybridized. The amide function can be illustrated in three dimensions by structure 4. The electronic distribution can also be viewed as the result of the delocalization of two n electron pairs, one from the oxygen atom and one from the nitrogen atom (cf. 1 and 3 versus 2) and on that basis, it is referred to here as the primary electronic delocalization of the amide function.



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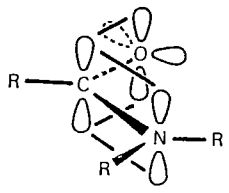

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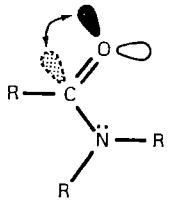

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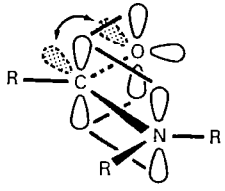

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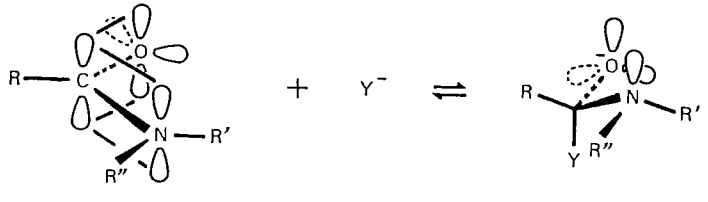
Furthermore, the oxygen atom of the carbonyl group in the amide function has an electron pair oriented antiperiplanar to the polar C − N bond; there is therefore an electronic delocalization caused by the overlap of that oxygen electron pair orbital with the antibonding orbital of the C − N sigma bond (σ*) as shown in two dimensions by structure 5 and in three dimensions by structure 6. This additional n-σ* delocalization is referred to here as a secondary electronic delocalization. Thus, amides are similar to E esters because they both have the primary electronic effect and one secondary electronic effect. This is in contrast with Z esters which have two secondary electronic effects besides the primary electronic effect.

As in the case of esters, formation of tetrahedral intermediates from amides must take place with stereoelectronic control (1). Under these conditions a nucleophile Y^- must make an approach almost perpendicular (i.e. with a ≈109° angle (5)) to the plane of the conjugated system of the amide, giving a tetrahedral intermediate which has an electron pair on both the oxygen and the nitrogen atom oriented antiperiplanar to the newly formed C − Y bond (4 → 7). Note that the R' − N bond remains antiperiplanar to the C − R bond in 7 and that the R" group of the nitrogen atom which was syn to the R group in 4 becomes gauche to it in 7. Consequently, the conversion 4 → 7 follows the principle of least motion (6-8).



4 7

The principle of microscopic reversibility predicts that the reverse process must follow the same path which is indeed stereoelectronically allowed: the oxygen atom in 7 has two secondary electronic effects (n-σ*) (one electron pair of the oxygen atom is antiperiplanar to the C − N bond while the other is antiperiplanar to C − Y bond) and the nitrogen has one (the nitrogen electron pair is antiperiplanar to the C − Y bond). Thus, there are three secondary electronic effects (n-σ*) in 7 and by the ejection of Y^- to form 4, two of these (due to the two electron pairs antiperiplanar to the C − Y bond) have been transformed into primary electronic effects (n-π*) in the product 4. The third secondary electronic effect remains a n-σ* interaction in the product. The ejection of Y^- can therefore take place with the help of the primary and one secondary electronic effects.

In cases where Y is an alkoxy group, there is the possibility of forming either an ester or an amide function, and the proportion of each will depend on the conformation of the tetrahedral intermediate. The nine different gauche conformers for such a hemi-orthoamide tetrahedral intermediate are shown in Fig. 1, and the stereoelectronically controlled cleavages are described in Table 1.

TABLE 1 Predicted Cleavages of the Nine Conformers of Hemi-orthoamide

amide	conformer	ester
″	A	
″	B	E
″	C	Z
	D	
	E	E
	F	Z
	G	
	H	E
	I	Z

A detailed examination of the cleavage in conformers A, B, and C follows. Interestingly these three are the only conformers generated directly from reaction of alkoxide ion on a tertiary amide, with stereoelectronic control. Cleavage of conformer A can only lead to the tertiary amide, as the ejection of the amino group cannot occur with the help of the primary electronic effect (the O − R bond is antiperiplanar to the C − N bond). Conformer B

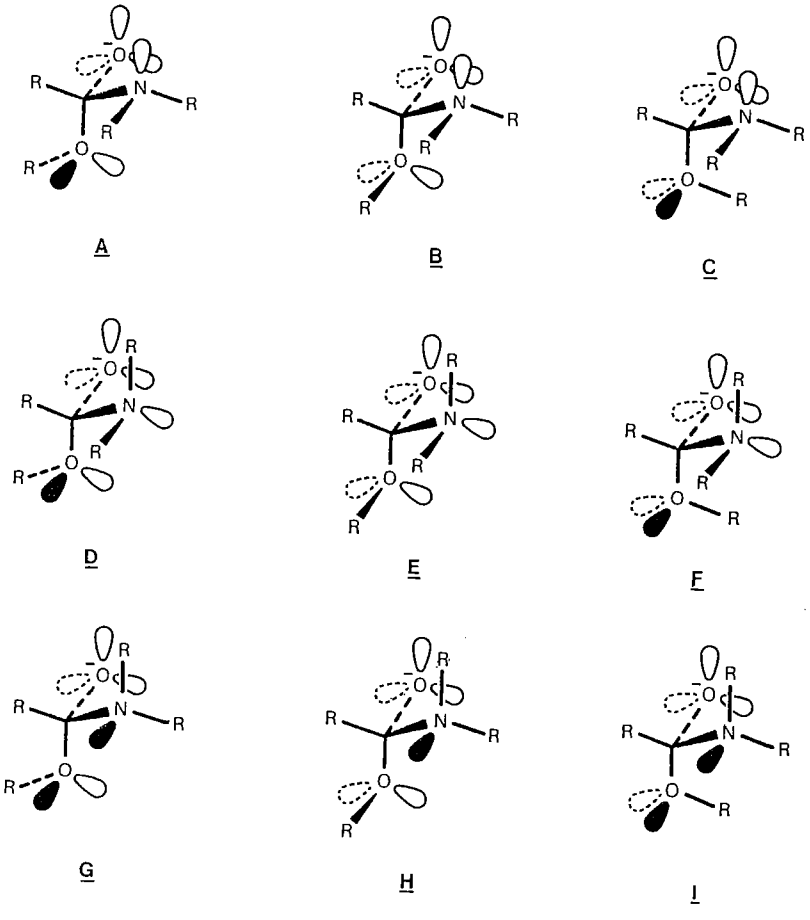


Fig. 1

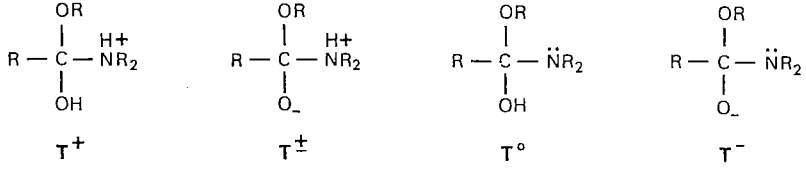
can give either the tertiary amide or an E ester whereas conformer C can yield either the tertiary amide or a Z ester.

In addition to the primary electronic effect, in conformer B, the ejection of the amino group and the OR group occur each with the help of one secondary electronic effect, while in conformer C, the cleavage of the amino group occurs with two secondary electronic effects and that of the OR group

with one. In conformer B, both cleavages are consequently equally favored electronically but since the OR group is a better leaving group, the formation of a tertiary amide should be favored. In conformer C, the ejection of the amino group is electronically favored by the additional secondary electronic effect. On that basis, the ejection of the amino group by comparison with the OR group should be easier.

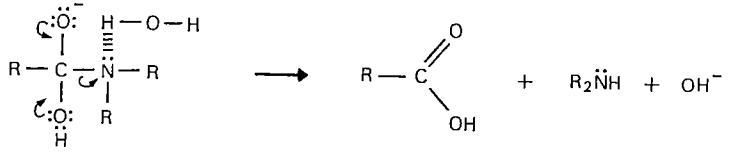
The secondary electronic effect can also influence the ability of a leaving group (cf. p. 32). The OR oxygen has one secondary electronic effect in conformer B and two in conformer C while the amino group has only one in both conformers. Thus, the OR oxygen has one double character in conformer B and two in conformer C. The OR group is thus a poorer leaving group in conformer C than in conformer B. This factor favors again the ejection of the amino group in conformer C by comparison with conformer B. Consequently, in conformer C, the secondary electronic effect makes the OR group a poorer leaving group and, at the same time, this effect favors the ejection of the amino group electronically. On that basis, it is possible to rationalize why an a priori poorer leaving group (R_2N^-) can be ejected in preference to a better leaving group.

The ionic state of the hemi-orthoamide tetrahedral intermediate must also be considered (9-12). In acidic medium, the intermediate will exist in the protonated form T^+, in slightly basic medium (near the pKa of T°, pH ≈ 10), it will exist as a mixture of T° and $T^{\pm}$, and in basic medium (pH > 11), it will exist as T^-.



The energy barrier for the breakdown of $T^{\pm}$ is much lower than that of T°; in $T^{\pm}$, the ammonium group is a good leaving group and the negatively charged oxygen should ease its ejection. Since the rate of proton transfer is a fast process (13), the interconversion T° ⇌ $T^{\pm}$ will be so fast that the cleavage of the neutral form T° need not to be considered since it will not take place.

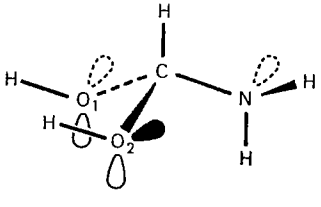
It is expected that the T^+ and $T^\pm$ ionic forms will always eject the amino group because the protonated nitrogen atom does not have an electron pair available to eject the alkoxy group and, the ammonium group is a much better leaving group than the alkoxy group. Ejection of the alkoxy group in competition with the amino group can occur in the T^- ionic form, where the cleavage of the C − N bond will take place only if the nitrogen electron pair is hydrogen bonded with the solvent (cf. 8) (14-18). Under such conditions, the amino group can leave as a secondary amine and the ejection of the high energy amide ion ($R_2\ddot{N}:^-$) is avoided.



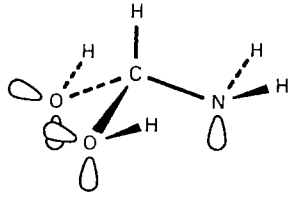
8

The relative energy barrier for stereochemical change from one tetrahedral intermediate to another and that for a stereoelectronically controlled cleavage must also be taken into consideration when analyzing experimental results. Evidence will be presented that in certain cases (specially when the tetrahedral intermediate exists in the T^- ionic form) conformational change of the intermediate does not compete with its cleavage.

Lehn and Wipff (19, 20) have reported an ab initio quantum chemical study of aminodihydroxy methane ($CH(OH)_2\ddot{N}H_2$) which indicates that there are marked stereoelectronic effects. They found that when there are two electron pairs antiperiplanar to the C − Y polar bond, the C − Y bond becomes long and weak. Also, the elongation of the C − Y bond is more pronounced when the atom Y does not have an electron pair antiperiplanar to a polar bond. For example, the C − N bond is short and strong in 9 and long and weak in 10; also, the C − O_2 bond in 9 is long and weak.



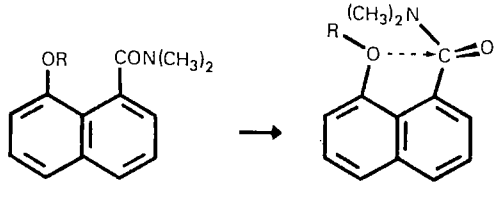
9



10

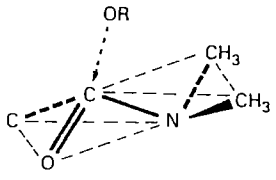
In another theoretical study (21) they have compared the neutral form T° of a hemi-orthoamide with the T^+ and the T^- ionic forms. Protonation leads to a marked and selective lengthening and weakening of the C − N bond, whereas the C − O bonds are slightly shortened and strengthened. The changes in C − N bond length show strong stereoelectronic conformation dependence; the forms where the C − N bond is antiperiplanar to two electron pairs have a very long and weak C − N bond. The C − O bond properties are also conformation dependent. They concluded that by comparison with the neutral T° form, the T^+ ionic form should lead to preferential C − N bond cleavage with higher reactivity and higher conformational selectivity. Also, deprotonation of an OH group lengthens and weakens the C − N bond. Both the C − N and the C − OH bonds should be cleaved in the T^- ionic form more easily than in the neutral T° form.

A very interesting observation was made by Dunitz and co-workers (22) in the crystal structure analyses of N,N-dimethyl-8-hydroxynaphthalene 1-carboxamide 11 and the corresponding methoxy derivative 12. The amide function is perpendicular to the aromatic ring, and is splayed outward while the C − OR bond is inward, i.e. toward the carbonyl group (cf. 13). The carbonyl naphthalene bond is bent in such a way to allow a better alignment of the oxygen nucleophile toward the carbonyl amide (5). There is also a small but significant pyramidalization of the carbonyl group carbon as well as the amide nitrogen but in the opposite direction; the carbonyl carbon atom is closest to the nucleophilic oxygen atom while the nitrogen atom displacement is away from it as illustrated in 14. This result is in complete agreement with the principle of stereoelectronic control in hydrolytic reactions.



11 R = H
12 R = CH_3

13

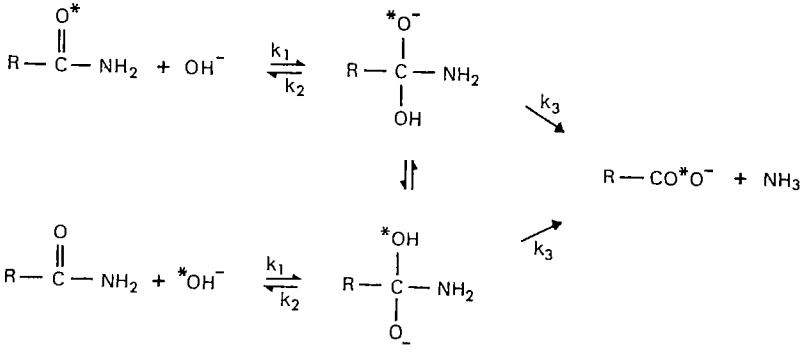


14

Further experimental evidence supporting the principle of stereoelectronic control in the cleavage of hemi-orthoamide tetrahedral intermediates has been obtained from studies on the carbonyl-oxygen exchange during the basic hydrolysis of amides, and from the hydrolysis of imidate salts. These experiments are described next.

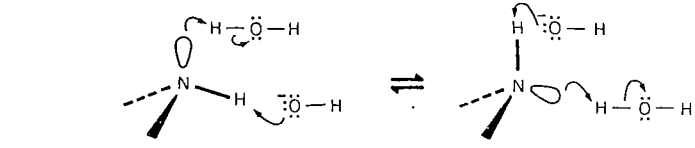
Carbonyl-oxygen exchange concurrent with hydrolysis in amides

Carbonyl-oxygen exchange has been observed in the course of the basic hydrolysis of primary amides (23, 24). The exchange, observed by using ^{18}O-labeling ($O^* = {}^{18}O$), occurs via a tetrahedral hemi-orthoamide intermediate and the extensive exchange observed was explained by the fact that k_2 is larger than k_3 because an OH group is a much better leaving group than an NH_2 group.



We will see that this technique can be used to demonstrate the importance of the principle of stereoelectronic control in tetrahedral intermediates derived from amides. Primary, secondary, and tertiary amides as well as N — H and N-alkyllactams will be examined.

The stereoelectronically controlled reaction of hydroxide ion with the ^{18}O-labeled primary amide 15* (R'=H) (Fig. 2) should form tetrahedral conformer 16 (R'=H) specifically. It is assumed that proton transfer on the two oxygens can take place prior to the breakdown of intermediate 16 (R'=H). The same assumption is also made for the proton transfer on the nitrogen. The conversion 16 (R'=H) → 17 (R'=H) is therefore allowed. The proton transfer on the nitrogen can occur with the solvent via the following process. Intermediate 16 (R'=H) has proper electron pair orientation (primary electronic effect) to give the starting amide 15* (R'=H) and the hydrolysis products or the unlabeled amide 15 (R'=H) via 17 (R'=H). As k_2 is larger than k_3 (OH being a better leaving group than NH_2), primary amides should exhibit significant exchange, a prediction which is supported by experiments (23, 24).



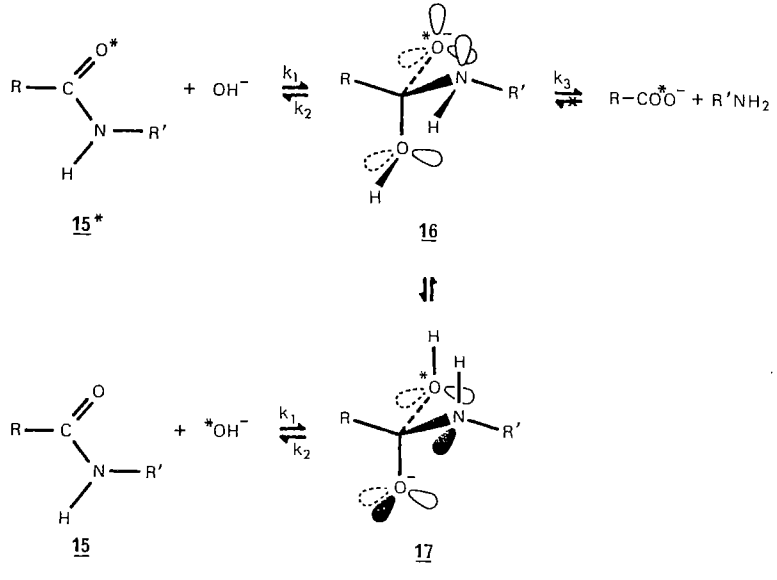


Fig. 2

A similar conclusion can be reached with secondary amides. In the most stable conformation for secondary amide, the alkyl group on the nitrogen atom is syn to the carbonyl-oxygen as in 15* (25, 26). The reaction of hydroxide should give 16 which can also be converted into 17. Thus, secondary amides should undergo carbonyl-oxygen exchange with the solvent during basic hydrolysis. This is also in accord with the experimental results (23, 24).

The fact that there is carbonyl-oxygen exchange in primary and secondary amides is in accord with the principle of stereoelectronic control but it does not constitute a proof since these experimental results can be explained without the use of this principle.

The stereoelectronically controlled reaction of hydroxide ion with an ^{18}O-labeled tertiary amide (18*) (Fig. 3) should give the intermediate 19 which can fragment in only two ways, yielding the starting labeled amide 18* or the hydrolysis products; direct cleavage of 19 to give unlabeled amide 18 cannot take place with the help of the primary electronic effect. In order to form the unlabeled amide 18 with stereoelectronic control, intermediate 19 must first be converted into another conformer such as 20. Oxygen

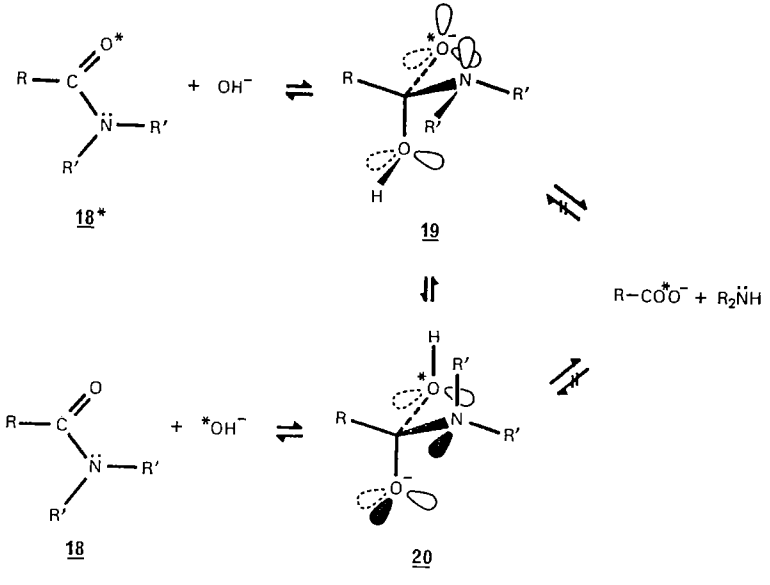


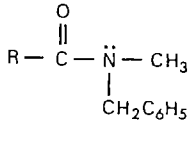
Fig. 3

exchange in tertiary amides depends therefore on the relative ease with which intermediate 19 can give either intermediate 20 or the hydrolysis products by direct fragmentation. Thus, the main difference between primary, secondary and tertiary amides, is that the first two can undergo ^{18}O-exchange without invoking a conformational change at the nitrogen in the corresponding tetrahedral intermediate, whereas in the case of tertiary amide, ^{18}O-exchange will take place only if conformational change at the nitrogen is allowed.

The change of 19 into 20 can be obtained either by a 120° rotation around the C – N bond, or by inversion of the nitrogen atom followed by a 60° rotation. Appropriate proton transfer on the two oxygens must also take place. For conformational change to occur at rates competitive with fragmentation, it is necessary that the energy barrier for that process be less than or comparable to that for fragmentation. Thus, there may or may not be oxygen exchange concurrent with the basic hydrolysis of tertiary amides, and that depends on the relative energy barriers for conformational change and fragmentation.

Bunton, Nayak, and O'Connor (27) have studied carbonyl-oxygen exchange during the hydrolysis of a primary, a secondary and a tertiary amide. They have observed that the alkaline hydrolysis of benzamide and N-methylbenzamide but not of N',N-dimethylbenzamide, is accompanied by extensive oxygen exchange between water and the amide. Thus, the tetrahedral intermediate (19, R'=CH_3 and R=C_6H_5) derived from N,N-dimethylbenzamide fragments more easily than it can undergo conformational change. The fact that there is no carbonyl-oxygen exchange in N,N-dimethylbenzamide constitutes a strong support for the principle of stereoelectronic control because this result can be rationalyzed only if that principle is taken into consideration.

The rates of hydrolysis and carbonyl-oxygen exchange carried out at 27°C with potassium hydroxide (1.5 N) on labeled N-benzyl-N-methyl derivatives of formamide (21), acetamide (22), and propionamide (23) have been reported (14).

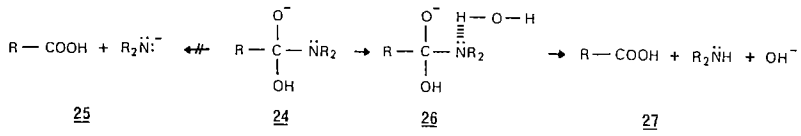


21 R = H
22 R = CH_3
23 R = C_2H_5

It was found that there is significant carbonyl-oxygen exchange in the formamide, very little in the acetamide and apparently none in the propionamide. Thus, as the R group increases in size (R=H, CH_3, C_2H_5), carbonyl-oxygen exchange is less favored. This observation can be readily explained. In intermediate 19, the barrier for internal rotation or inversion of the amino group should be lower when R is small and higher when R is large. At the same time, the energy barrier for the breakdown of 19 should be higher when R is small and lower when R is large. When R is a large group, it should favor the breakdown of the intermediate due to steric decompression. The reverse of this steric decompression effect is the classical steric hindrance caused by the size of the R group in esters ($R-COOR'$) and amides ($R-CONR'_2$) which influences the rate of hydrolysis. For instance, formamides are hydrolyzed more rapidly than acetamides. Thus, as the R group in intermediate 19 increases in size, there should be less conformational change and that should result in decreasing carbonyl-oxygen exchange, and this is in accord with the experimental results.

The rates of carbonyl-oxygen exchange and hydrolysis of these three tertiary amides were also measured at higher temperatures (45, 65, 90°C) and it was observed that the increase in the rate of oxygen exchange is greater than that of hydrolysis with an increase of temperature (14). For instance, at 27°C, N-benzyl-N-methylformamide is hydrolyzed at a faster rate than it undergoes cabonyl-oxygen exchange, but at 90°C, the reverse is true; oxygen exchange occurs at a faster rate than hydrolysis. In principle, an increase in temperature should enhance the rate of breakdown of the intermediate as well as that of conformational change. The large increase in rate of one process over that of the other may appear surprising as both are essentially of the same nature involving internal molecular motion. There must therefore be an entropy factor which should either disfavor the breakdown of the tetrahedral intermediate or favor the conformational change with an increase of temperature.

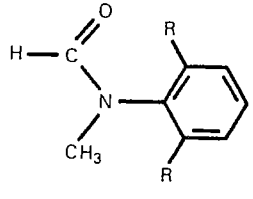
When a hemi-orthoamide tetrahedral intermediate exists in the $T^{\pm}$ ionic form, the amide ion is not ejected previous to protonation by the solvent, to give the secondary amine. The formation of an amide ion 24 → 25 is a process so high in energy, that both the protonation and the ejection processes must be synchronized 24 → 26 → 27 (28). This means that in aqueous solution, the nitrogen electron pair must first be hydrogen bonded with the solvent, so that the group can leave as a secondary amine.



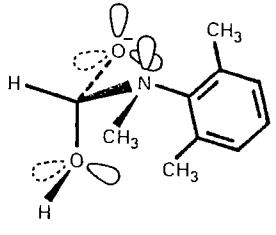
25 24 26 27

Thus the tetrahedral intermediate must first be hydrogen bonded with the solvent before the breakdown can occur. The hydrogen bond to the nitrogen will be clearly favored at low temperature and disfavored at higher temperatures. On that basis, the breakdown of the intermediate is favored at low temperature and disfavored at higher temperature. At the same time, conformational changes should be easier at higher temperature (less hydrogen bonds) than at low temperature. Thus, by taking into account the importance of hydrogen bonding to the nitrogen in the tetrahedral intermediate, the increase of the rate of oxygen exchange over the rate of hydrolysis with an increase of temperature is readily explained.

A clear demonstration of the importance of a hydrogen bond to the nitrogen was obtained by studying N-2,6-dimethylphenyl-N-methylformamide (28) (14) and N-methyl-N-phenylformamide (29). The essential difference between these two formamides is believed to be that in 28, contrasting to 29, the benzene ring is not conjugated with the amide function. The benzene ring in 28 is perpendicular to the plane of the amide function. X-Ray analysis of an imidate salt derived from 28 supports this assignment (vide infra, p. 121). Interestingly, formamide 28 does not hydrolyze (0.15 N, KOH, 90°C, 70 h) but undergoes considerable carbonyl-oxygen exchange (>90%). This is in contrast with N-methyl-N-phenylformamide (29) where the hydrolysis as well as the carbonyl-oxygen exchange proceeded with ease. Formamide 28 must form the tetrahedral intermediate 30 as it undergoes carbonyl-



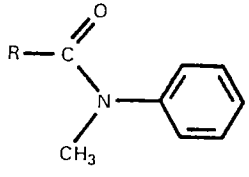
28 R = CH_3
29 R = H



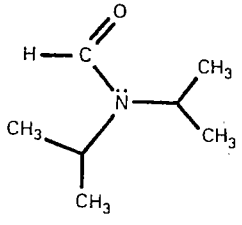
30

oxygen exchange, but since the hydrogen bonding to the nitrogen in 30 is prevented by the presence of the two methyl groups on the phenyl ring (which is parallel with the nitrogen electron pair) cleavage of the C — N bond does not take place.

The hydrolyses of labeled N-methyl-N-phenyl derivatives of acetamide (31) and of propionamide (32) were also carried out (14). It was found that there is appreciable oxygen exchange at 27°C in the N-methyl-N-phenylamides 31 and 32 which was not the case for the N-benzyl-N-methylamides 22 and 23. This difference in behavior between these two types of amides can be explained by the phenyl ring in 31 and 32 which can be conjugated with the amino group in the tetrahedral intermediate. This conjugation effect must lower the barrier for nitrogen inversion. As a consequence, one of the two possible modes for conformational change at the nitrogen atom, i.e. nitrogen atom inversion plus a rotation of 60°, will be a lower energy process. At the same time, the amino group is less basic, and should therefore be weakly hydrogen-bonded with the solvent so the inversion-rotation process will again be favored.



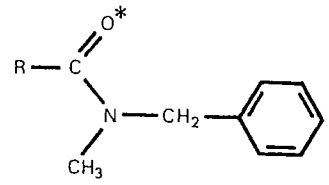
31 R = CH_3
32 R = C_2H_5



33

It was also found that N,N-diisopropylformamide 33 is hydrolyzed slowly but undergoes extensive oxygen exchange (14). In 33, the hindrance caused by the presence of the two isopropyl groups must slow down the rate of formation of the tetrahedral intermediate. The isopropyl groups must also create steric hindrance for hydrogen bonding in the tetrahedral intermediate. The cleavage of the tetrahedral intermediate becomes unusually difficult and conformational change is thus favored over that of hydrolysis in this case.

The rates of hydrolysis and carbonyl-oxygen exchange of ^{18}O-labeled N-benzyl-N-methylamides 34 (R=H, CD_3 and CD_2CH_3) were carefully measured at several temperatures in $D_2{}^{16}O$ (18). The activation parameters, found by plotting



34

$\ell n(k/T)$ versus $1/T$ where k is the second order rate constant for hydrolysis (k_h) or exchange (k_{ex}), are summarized in Table 2. The activation parameters for hydrolysis ($\Delta H_h^{\neq}$, $\Delta S_h^{\neq}$ and $\Delta G_h^{\neq}$) are in accord with values obtained previously on similar amides (12, 29). The large negative entropy of activation indicates that the nitrogen in the tetrahedral intermediate must form a hydrogen bond with the solvent in order for hydrolysis to occur. As expected, the formamide is more reactive towards hydrolysis than the other amides.

TABLE 2 Activation Parameters for Hydrolysis and ^{18}O Exchange of Amides 34

R	$k_h^{25°a}$ (ℓ mol^{-1} s^{-1})	$\Delta H_h^{\neq}$ (kcal mol^{-1})	$\Delta S_h^{\neq}$ (eu)	$\Delta G_{h-25°}^{\neq}$ (kcal mol^{-1})	$k_{ex}^{25°a}$ (ℓ mol^{-1} s^{-1})	$\Delta H_{ex}^{\neq}$ (kcal mol^{-1})	$\Delta S_{ex}^{\neq}$ (eu)	$\Delta G_{ex-25°}^{\neq}$ (kcal mol^{-1})
H	1.15×10^{-4}	12.4±0.3	-34.9±0.5	22.8	3.56×10^{-5}	15.3±0.6	-27.5±1.9	23.5
CD_3	2.75×10^{-6}	13.3±0.2	-39.3±0.5	25.0	1.54×10^{-7}	19.0±0.3	-25.9±0.9	26.7
CH_3CD_2	1.27×10^{-6}	13.4±0.5	-40.5±1.3	25.5	6.85×10^{-8}	20.7±1.0	-21.8±2.8	27.2

[a] Extrapolated.

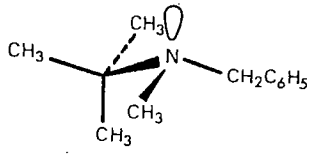
Comparison of the activation parameters for carbonyl-oxygen exchange and for hydrolysis shows that, for the formamide, the rate of exchange is only slightly lower than that of hydrolysis, whereas in the case of acetamide and propionamide, the exchange occurs at a significantly lower rate.

Using the equilibrium constants estimated by Guthrie (12) for hemi-orthoamide tetrahedral intermediates (derived from N,N-dimethylformamide and N,N-dimethylacetamide) and the activation parameters described in Table 2, it was possible to obtain the free energy of activation for the breakdown ($\Delta G_{cleav}^{\neq}$) and for conformational change ($\Delta G_{conf}^{\neq}$) of the tetrahedral intermediates derived from the N-benzyl-N-methyl derivatives of formamide, acetamide and propionamide. These values are the following.

	$\Delta G_{cleav}^{\neq}$ (kcal/mol)	$\Delta G_{conf}^{\neq}$ (kcal/mol)
formamide	5.2	5.8
acetamide	6.2	8.0
propionamide	6.5	8.2

The free energy of activation for the breakdown ($\Delta G^{\neq}_{cleav}$) does not vary considerably with the amide structure, while that for the conformational change at the nitrogen ($\Delta G^{\neq}_{conf}$) changes appreciably from the formamide to the acetamide (or propionamide). This confirms that the conformational step is influenced appreciably by the steric interaction of the R group in these N,N-dimethylamides.

It is interesting to compare tert-butylbenzylmethylamine (35) with the tetrahedral intermediate 36 derived from N-benzyl-N-methylacetamide which has a similar degree of substitution. The rotation barrier for the $(CH_3)_3C-N$ bond and the nitrogen inversion barrier in 35 have been found identical and estimated at 6.2 kcal/mol (30). The higher value of 8.0 kcal/mol for the intermediate 36 must be a consequence of the double-bond character of the C – N bond (nitrogen atom has one secondary electronic effect (n-σ*)).



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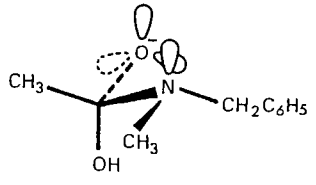
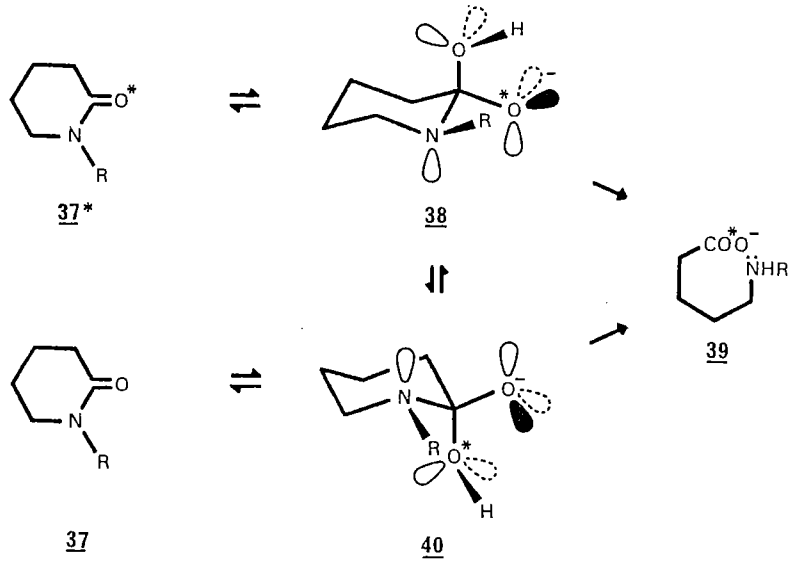


36

Lactams have also been studied (31). ^{18}O-Labeled N-alkyllactams 37* (Fig. 4) must react with hydroxide ion to give the tetrahedral intermediate 38 which can either revert to labeled lactam 37* or produce the aminocarboxylic acid salt 39; intermediate 38 cannot give unlabeled lactam 37 with primary stereoelectronic control. Unlabeled lactam 37 can be obtained only if the tetrahedral conformer 38 can undergo a chair inversion and proton exchange to give conformer 40. Indeed, conformer 40 can give unlabeled lactam 37 with stereoelectronic control. Thus, carbonyl-oxygen exchange should be observed in N-alkyllactams only if the energy barrier for the chair inversion (38 ⇌ 40) can compete with the breakdown (38 → 39).

A similar conclusion can be reached with N – H lactams (37*, R=H). Such lactams should give intermediate 38 (R=H). Again, 38 can only yield either 37* (R=H) or 39 (R=H). Unlabeled lactam 37 (R=H) can be obtained only via conformer 40 (R=H). Thus, as in the case of N-alkyllactams, N – H lactams will undergo carbonyl-oxygen exchange only if the conformational change

38 ⇌ 40 and proton exchange can compete with the cleavage of intermediate 38 to give the hydrolysis product 39 (R=H).



37* 38 39 37 40

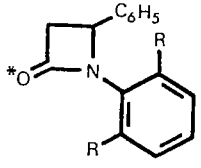
Fig. 4

^{18}O-Labeled N-methylpiperidone (37*, R=CH_3) and ^{18}O-labeled piperidone (37*, R=H) have been studied (31) and it was found that basic hydrolysis (1 N, NaOH) at room temperature occurs readily but no carbonyl-oxygen exchange was observed. These results show clearly that the conformational change 38 ⇌ 40 (R=H or CH_3) cannot compete with the breakdown of 38 to yield the hydrolysis product 38 (R=H or CH_3). Again, these results are consistent only if the principle of stereoelectronic control is taken into consideration; indeed, if it is neglected, 37* should give directly 40 as well as 38.

It is interesting to point out that N–H lactams which are secondary amides react differently (no ^{18}O-exchange) from acyclic secondary amides. This difference in behavior can however be readily explained because acyclic secondary amides exist in a different conformation (Z) from N – H lactams which are locked in the E conformation. Indeed, oxygen exchange can occur without conformational change, i.e. via appropriate oxygen and nitrogen

proton transfers with the solvent, only in tetrahedral intermediates derived from secondary amides having the Z conformation.

β-Lactams 41* and 42* have also been studied (17). Concurrent carbonyl-oxygen exchange upon hydrolysis was not observed with β-lactam 41*. The β-lactam 42* is hydrolyzed at a considerably slower rate than the β-lactam 41* and contrary to 41*, 42* does undergo concurrent carbonyl-oxygen exchange.



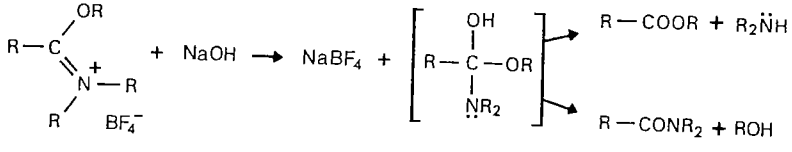
41* R = H

42* R = CH_3

The result obtained with β-lactam 41* shows that the corresponding tetrahedral intermediate cleaves more readily to the hydrolysis product rather than undergo a conformational change. The result obtained with β-lactam 42* can also be readily explained: 42* can form a tetrahedral intermediate. However, the barrier to ring opening to give the hydrolysis product is raised in this case because of the steric hindrance to hydrogen bonding with the solvent (caused by the two methyl groups on the phenyl group). Conformational change can therefore compete with hydrolysis, with the result that carbonyl-oxygen exchange is observed.

Hydrolysis of imidate salts

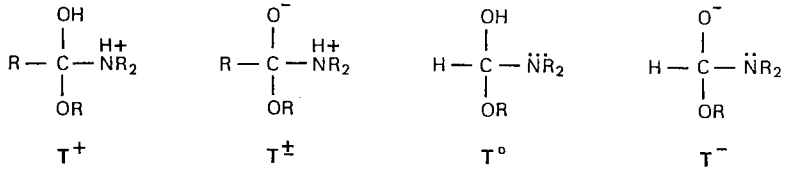
Imidate salts are O-alkyl derivatives of tertiary amides. Being activated tertiary amides, they are extremely reactive towards nucleophiles. There is instantaneous reaction with hydroxide ion; they also react rapidly at room temperature with water under acidic conditions. When an imidate fluoroborate salt such as 43 reacts with sodium hydroxide, it gives sodium fluoroborate and the tetrahedral intermediate 44 which breaks down in an irreversible manner to yield the products of the reaction which can be either the corresponding ester and amine or amide and alcohol. The formation of 44 has been verified with ^{18}O-labeling experiments.



43 44

The hydrolysis of imidate salts is a technique to generate in situ hemi-orthoamide tetrahedral intermediates (44), and to observe their breakdown to yield the reaction products under kinetically controlled conditions. Such conditions can be ascertained by verifying that the reaction products are not interconverted (amide + alcohol ≠ ester + amine) during the reaction. This technique can therefore be used to test the principle of stereoelectronic control in the cleavage of tetrahedral intermediates derived from amides.

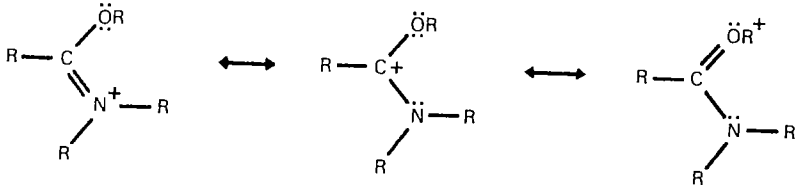
A hemi-orthoamide tetrahedral intermediate can take several ionic forms, T^+, $T^\pm$, T°, and T^-, depending on the pH of the reaction medium. In acidic medium, it will exist in the T^+ form, in slightly basic medium (near the pKa of the intermediate, pH ≈ 10), it will exist as $T^\pm$ and in basic medium (pH > 11), as T^-. In systems where the nitrogen can be readily protonated, T° is neglected since it is rapidly converted into the $T^\pm$ form which has a low energy barrier for fragmentation.



T^+ $T^\pm$ T° T^-

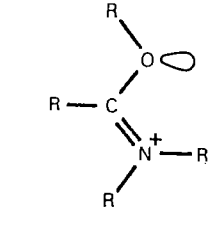
We have already discussed (p. 106) that T^+ and $T^\pm$ ionic forms can give the ester and amine products only. Thus, in acidic and neutral media which favor the formation of T^+ and $T^\pm$, imidate salts should always give the ester and amine products. In basic medium, which favors the formation of T^-, there is the possibility for the formation of both types of products, i.e., ester and amine or amide and alcohol. The cleavage of the C—N bond in the T^- tetrahedral intermediate will take place only if the nitrogen electron pair can form a hydrogen bond with a solvent molecule. Thus, experimental evidence in favor of the principle of stereoelectronic control can be obtained with imidate salts, only when the hydrolysis is carried out under basic conditions.

As in tertiary amides, the primary electronic effect (n-π^*) in imidates corresponds to the delocalization of two electron pairs, one from the nitrogen and one from the oxygen atom, which is normally represented by resonance structures 45, 46, and 47. The central atoms (C, N, and O) of the imidate function are therefore sp^2 hybridized and this is confirmed by X-ray analysis (32) which shows that this function is planar. As a consequence, an imidate function can exist in two different conformations, the anti or the syn form.



45 46 47

The syn and the anti forms can be represented in two dimensions by structures 48 and 49, and in three dimensions by structures 50 and 51 respectively. In the syn conformation, the O — R bond is syn to the C — R bond



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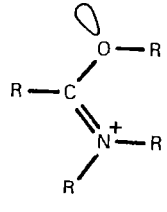

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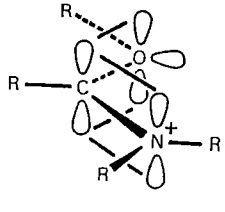

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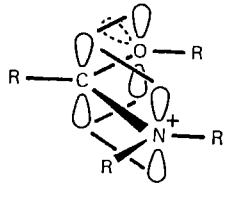
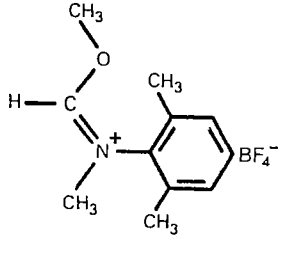


51

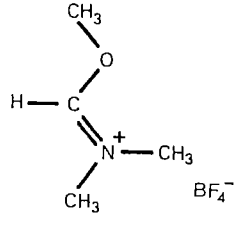
whereas in the anti conformation, the O — R bond is antiperiplanar to the C — R bond.

In the anti conformation, the second electron pair on the oxygen atom (cf. 49 and 51) is oriented antiperiplanar to the polar C — N bond, so this electron pair orbital can overlap with the antibonding orbital (σ^*) of the C — N sigma bond. Thus, contrary to the syn isomer, anti imidates have in addition to the primary electronic effect, one secondary electronic effect (n-σ^*). This additional electronic delocalization should stabilize the anti form relative to the syn form.

Steric effects must also be taken into consideration. In the anti form, there is a severe steric interaction between the R group on the oxygen and one of the R groups on the nitrogen atom. In the syn form, there is a steric interaction between the R group of the oxygen and the R group on the carbon atom. When the R group on the carbon atom is small (R=H), the steric interaction in the syn form is minimized and this form predominates. X-Ray analysis (32) of imidate salt 52 of N-2,6-dimethylphenyl-N-methylformamide confirms this conclusion and further shows that the 2,6-dimethylphenyl group is orthogonal to the imidate function. It was also shown (11, 15, 33) by a nuclear Overhauser effect study that the formamide imidate salt 53 exists in the syn form in solution.

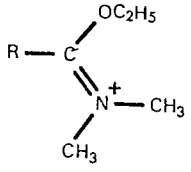


52



53

When the R group linked to the carbon atom is a large group (such as a t-butyl or a phenyl group conjugated with the imidate function), it is assumed that the anti form predominates. When that R group is of an intermediate size ($R=CH_3$ or cyclohexyl), it is assumed that there is a mixture of the syn and the anti forms. These assumptions are supported by the results obtained from the hydrolysis of imidate salts 54-57 (11).



54 R = CH_3

55 R = C_6H_{11}

56 R = C_6H_5

57 R = $(CH_3)_3C$

The results of hydrolysis of these imidate salts as a function of pH are the following: at pH 8.5 or lower, the imidate salts 54 and 55 yield the ester and amine products exclusively. At pH greater than 8.5, they start to produce the amide and alcohol products which reach a maximum yield at pH 11 (20% for 54 and 25% for 55), and this yield remains unchanged at higher pH. The imidate salts 56 and 57 behaved completely differently as they give exclusively the ester and amine products over the entire range of pH values.

These results confirm that under acidic or neutral conditions, the hydrolysis of imidate salts yield only the ester and amine products via the T^+ and $T^{\pm}$ ionic form. They also show that under basic conditions some imidate salts (56 and 57) yield only the ester and amine product whereas others (54 and 55) give a mixture of ester and amine plus amide and alcohol products. This difference in behavior of imidate salts can be readily explained by taking into account the principle of stereoelectronic control and by assuming that imidate salts 56 and 57 exist in the anti conformation whereas imidate salts 54 and 55 exist either in the syn conformation or as a mixture of the syn and anti conformations.

Application of the principle of stereoelectronic control to the hydrolysis of syn and anti imidate salts leads to the following analysis. Syn imidate salts are first considered.

The stereoelectronically controlled reaction of the syn imidate salt 58 (Fig. 5) with hydroxide ion must give specifically conformer 59, in which the nitrogen and the oxygen of the OR group have each an electron pair antiperiplanar to the C – OH bond; also, the R groups on the central carbon and on the oxygen atom which were syn in 58 are gauche in 59.

Intermediate 59 cannot eject the OR or the NR_2 group with stereoelectronic control. It is therefore assumed that the energy barrier for the fragmentation of 59 is too high and this process cannot compete with internal molecular rotation. Thus, 59 would undergo conformational changes either at the OR or NR_2 groups yielding in principle a mixture of the nine conformers described in Fig. 1 (p. 104, where 59 corresponds to conformer G). Thus, a syn imidate salt would first form intermediate 59 which is then converted into a mixture of several conformers some of which give the ester and amine, others the amide and alcohol products. For example, intermediate 59 would give intermediate 60 by rotation of the OR group and intermediate 61 by rotation of the NR_2 group. A stereoelectronically controlled fragmentation of the T^- ionic form of 60 can only give the ester and amine products where-

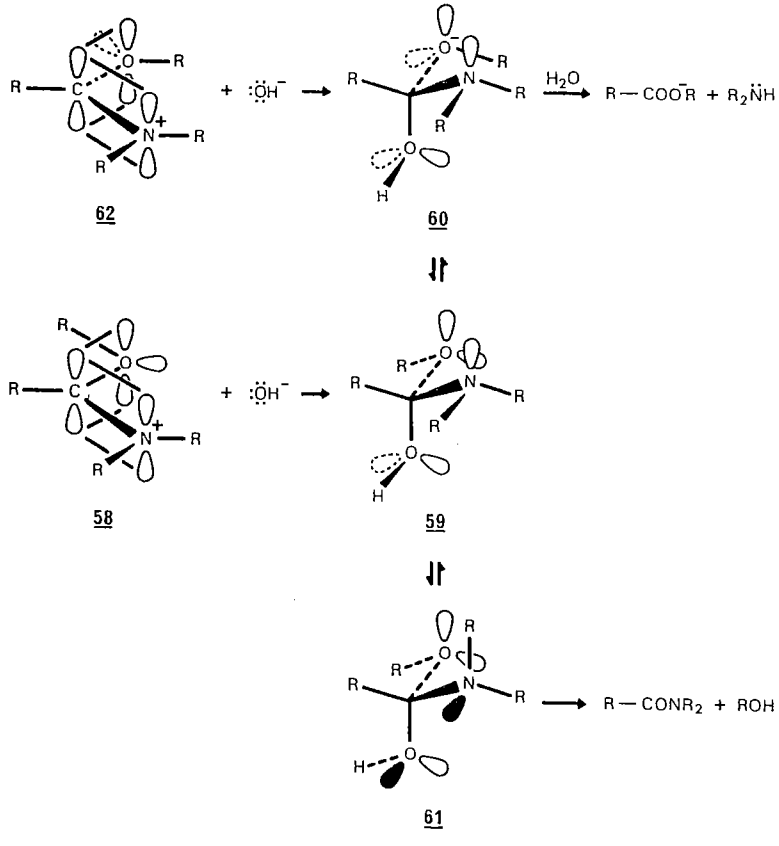


Fig. 5

as that of 61 can only yield the amide and alcohol products. Thus, the basic hydrolysis of syn imidate salts should give ester and amine plus amide and alcohol as products.

The stereoelectronically controlled reaction of hydroxide ion with an anti imidate salt (62) must give the hemi-orthoamide conformer 60 where the nitrogen and the oxygen of the OR group have each an electron pair antiperiplanar to the C − OH bond; also, the O − R bond and the N − R bond which were antiperiplanar to the C − R bond in anti imidate salt 62 remain in the same relative orientation in intermediate 60.

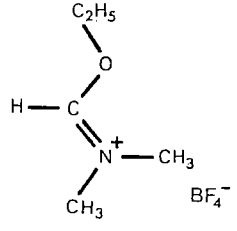
We have just seen that intermediate 60 can only give the ester and amine products under stereoelectronically controlled conditions. Consequently, in cases where the energy barrier for cleavage of the C − N bond is lower than that for conformational changes, the ester and amine should be the exclusive products of the reaction of hydroxide ion with anti imidate salts. In cases where the energy barrier for conformational changes is lower than that for fragmentation, intermediate 60 would then give in principle a mixture of the nine different conformers of Fig. 2 (where 60 corresponds to conformer I). Under such conditions, anti imidate salts also would give a mixture of ester and amine plus amide and alcohol products.

Thus, the results obtained with imidate salts 56 (R = C_6H_5) and 57 (R = $(CH_3)_3C$), i.e. exclusive formation of the ester and amine products, can be readily explained provided that they exist in the anti conformation, and that the energy barrier for fragmentation of the corresponding intermediate 60 is lower than that for conformational changes. This analysis is completely consistent with the study on the ^{18}O-carbonyl-oxygen exchange which showed that when the R group (R − $CONR_2'$) of a tertiary amide is large, conformational change cannot compete with fragmentation at room temperature. Also, this is in agreement with the fact that when the R group is large, imidate salts should exist in the anti conformation.

The mixture of ester and amine plus amide and alcohol products obtained from the imidate ion 54 (R=CH_3) and 55 (R=C_6H_{11}) can also be explained. These ions could exist in the anti form only. However, this would be surprising on the basis of the steric argument discussed previously. Also, the results obtained from the carbonyl-oxygen exchange in tertiary amides definitely show that conformational change can easily compete with the breakdown at room temperature only when R=H in tertiary amide ($RCONR_2'$). Thus,

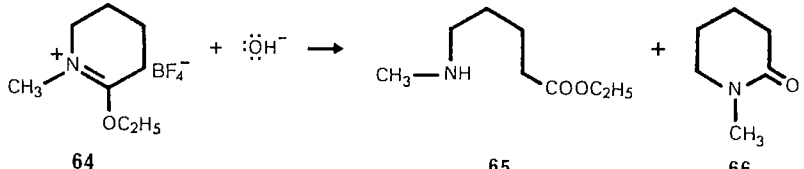
this possibility must be eliminated. These ions can exist either exclusively in the syn or as a mixture of syn and anti isomers. These two possibilities are likely because both predict the same results which correspond to the experimental observation. Indeed, if these ions are syn, it means that the intermediate 59 will first be produced and then, it would give different conformers which would yield the mixture of ester and amine plus amide and alcohol products. If these ions are a mixture of anti and syn, the former will give the ester and amine products whereas the latter would give a mixture of ester and amine plus amide and alcohol products.

This is also consistent with the results obtained from the basic hydrolysis of formamide imidate salt 63 (33) for which there is evidence (cf. 53) that this compound exists in the syn conformation. This salt gave a ≈1:1 mixture of ethyl formate and N,N-dimethylformamide.



63

The basic hydrolysis of imidate salt 64 was carried out (33), and it gave a mixture of aminoester 65 (83%) and N-methylpiperidone (66) (17%). This result can be explained in the following way. Assuming that this salt exists as a mixture of the syn and anti forms 67 and 68 (Fig. 6), these two isomeric forms would give the tetrahedral conformers 69 and 70 respectively. Conformer 70 can yield the aminoester 65 with stereoelectronic control whereas conformer 69 cannot break down. Thus, 69 would either be converted into 70 and 71 by rotation of the ethoxy group or undergo a chair inversion to conformer 72. Interestingly, 71 as well as 70 which come from the rota-



64 65 66

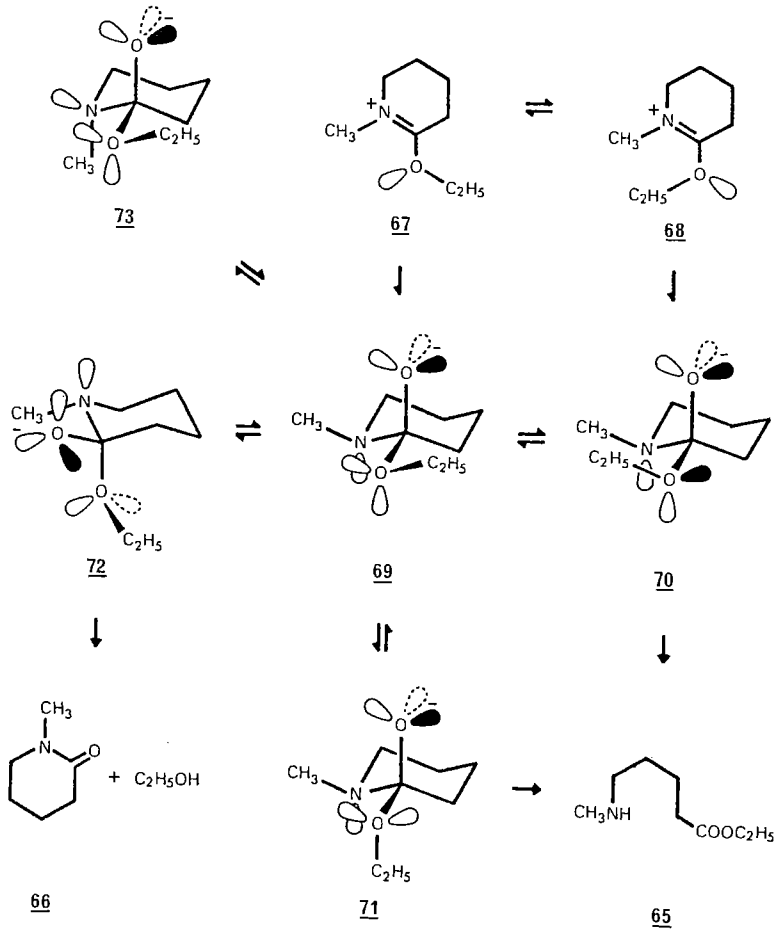
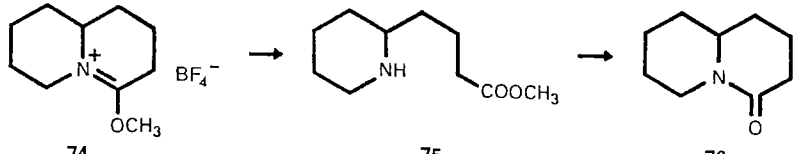


Fig. 6

tion of the ethoxy group can only give the aminoester 65, whereas conformer 72 which comes from the chair inversion can give N-methylpiperidone (66). The chair inversion should be a higher energy process than the ethoxy group rotation and on that basis a large percentage of aminoester is expected. Note that a simple nitrogen inversion in 69 yields the intermediate 73 which cannot break down with stereoelectronic control.

The above rationalization is confirmed by the study of imidate salt 74 which can be considered a bicyclic analog of imidate salt 64. Contrary to 64, bicyclic imidate salt 74 gave first only the aminoester 75 (33). The bicyclic lactam 76 appeared only after a certain time in the reaction mixture, indicating that the aminoester 75 is clearly the exclusive kinetic product of the rotation. As in the case of imidate salt 64, the bicyclic imidate salt must exist as a mixture of the syn and anti isomeric forms 77 and 78 (Fig. 7). The reaction of hydroxide ion with 77 and 78 must give the intermediates 79 and 80 respectively. Intermediate 80 can yield the aminoester 75. Intermediate 79 cannot break down with stereoelectronic control; it will therefore be converted into 80 or 81 which can also fragment to give the aminoester 75. Intermediate 79 can also undergo a nitrogen inversion by inverting ring A or ring B giving respectively intermediate 82 or 83. Intermediate 82 cannot undergo a C—N bond cleavage with stereoelectronic control. Intermediate 83 can yield the bicyclic lactam 76 with stereoelectronic control, but this intermediate has a severe steric interaction between the axial methoxy group and ring A. The formation of 80 or 81 from 79 should be a much easier process than that of 83, and on that basis, imidate salt 74 should give exclusively the aminoester 75, in agreement with the experimental result.



74 75 76

The formation of bicyclic lactam 76 from the aminoester 75 must also take place with stereoelectronic control. It presumably occurs from the intermediate 84 which comes from the cyclization of the aminoester 75 where the ester function is in the Z conformation (cf. 85). Note that the direct formation of 84 from the imidate salt 74 is impossible unless the principle of stereoelectronic control is violated.

The basic hydrolysis of imidate salt 86 was also reported (33). This salt gives a mixture of aminoester 87 (65%) and lactam 88 (35%). This result can be interpreted in the same manner as that of imidate salt 64.

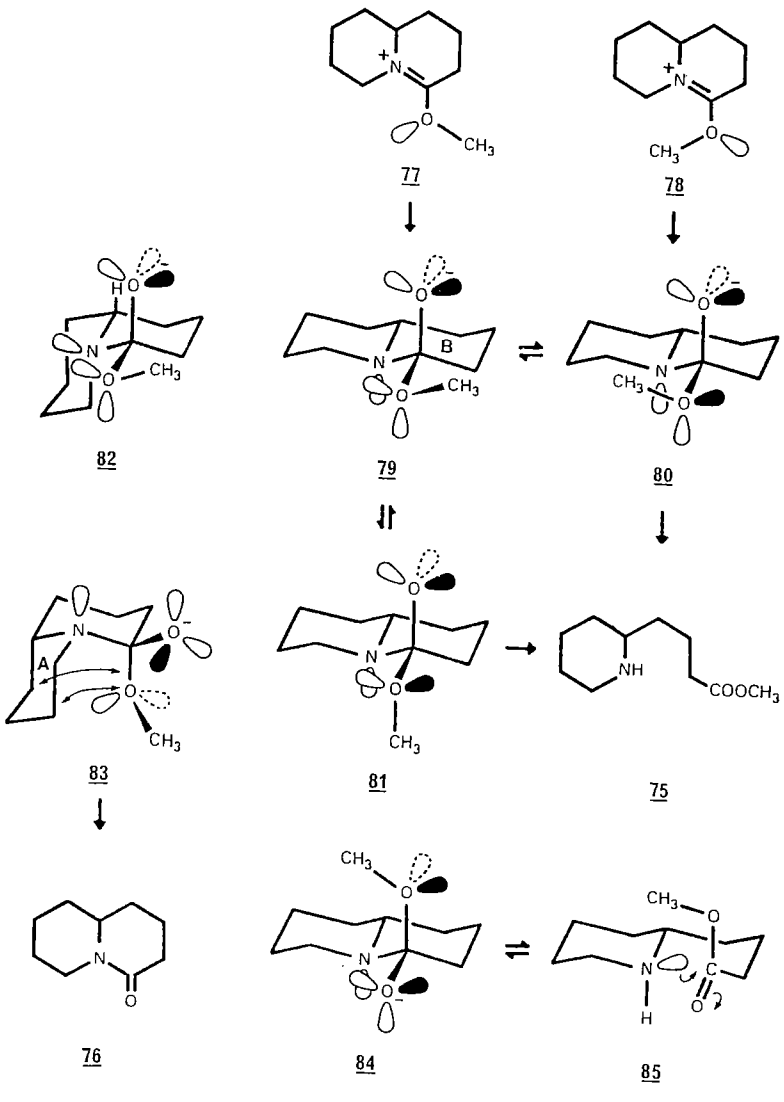
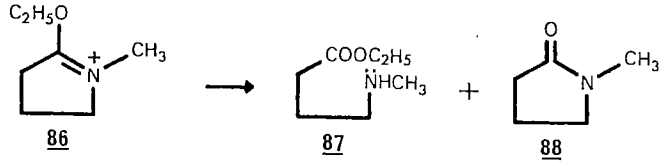


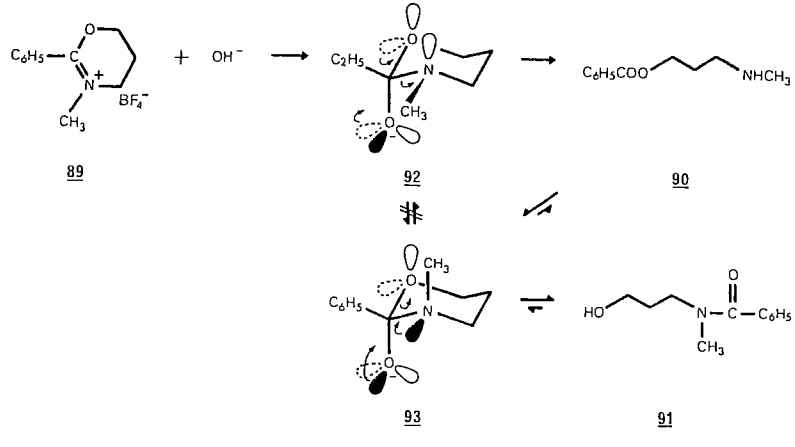
Fig. 7



The preceding results obtained from the various imidate salts can be correctly interpreted by taking into account the principle of stereoelectronic control. They constitute good evidence of its all important role, but they cannot be considered as absolute proof because the conformation of the imidate salts has not been thoroughly established.

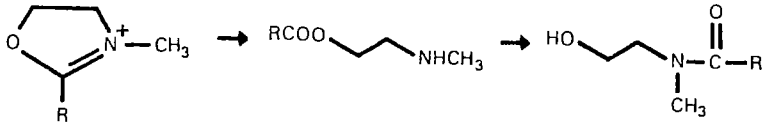
The results which follow have been obtained on imidate salts where there is absolutely no doubt about the syn or anti conformation, and they are in complete accord with the preceding rationalization.

The basic hydrolysis of a series of cyclic anti imidate salts has been investigated (1, 33). For instance, the six-membered imidate salt 89 where the anti conformation is assured by its cyclic structure, gave first under basic conditions, only the aminoester 90. The aminoester 90 was then slowly converted into the thermodynamic product of the reaction, i.e. the benzamidoalcohol 91. The reaction of imidate salt 89 with hydroxide ion must first give intermediate 92 following the principle of stereoelectronic control. It can also be seen that 92 can only give the aminoester 90 by following



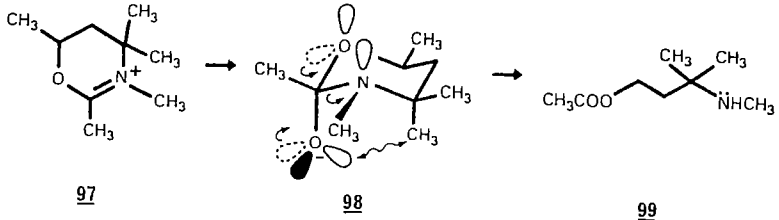
the same principle. Thus, the nitrogen inversion process to give 93 which can then yield the benzamidoalcohol 91 cannot compete with the breakdown of 92. The slow appearance of benzamidoalcohol 91 would be due to the slow formation of intermediate 93 from aminoester 90.

Similar studies were carried out (33) with cyclic imidate salts 94 (R=C_6H_5 or CH_3). They behaved like imidate salt 89, yielding first the aminoester 95 followed by the slow formation of the thermodynamic product, i.e. the corresponding amidoalcohol 96.

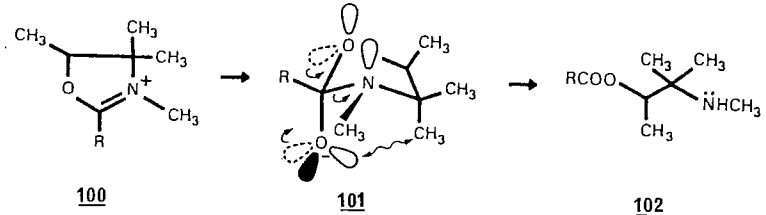


94 95 96

Imidate salt 97 also gave the aminoester 99 (33). Allen and Ginos (34) have reported that the basic hydrolysis of imidate salts 100 (R=CH_3, C_2H_5 or $(CH_3)_3C$) yielded only the corresponding aminoester 102.



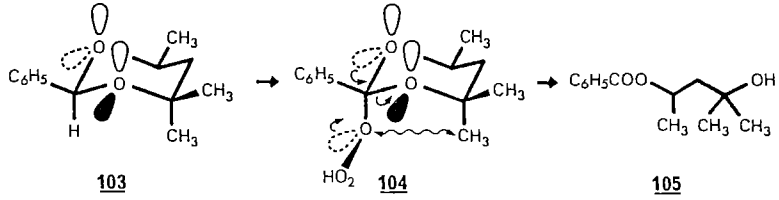
97 98 99



100 101 102

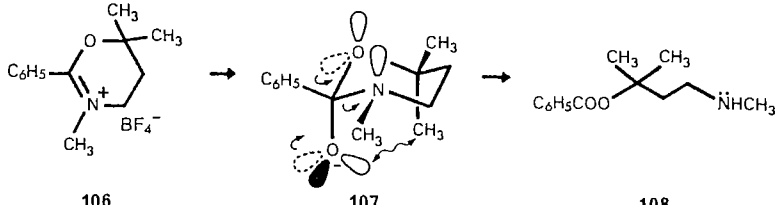
There are two factors which help the cleavage of the C—N bond in the hydrolysis of imidate salts 97 and 100. Imidate salt 97 should form the intermediate 98 which has proper electron pair alignment to yield the aminoester 99. Also, in 98 there is a 1,3-diaxial steric interaction between the OH group and one of the methyl groups which should promote the cleavage of the carbon-nitrogen bond. Similarly, compound 100 should give intermediate 101 in which there is again a strong steric interaction. This, combined with the stereoelectronic effect, favors the carbon-nitrogen bond cleavage.

The importance of this steric effect was verified by carrying out the ozonolysis of acetal 103. Oxidation of 103 by ozone gave the ester 105 exclusively (33). In this reaction, the hydrotrioxide intermediate 104 has proper electron pair orientation to favor the opening in both directions, but cleavage occurs in only one, yielding 105 because of this steric decompression factor.

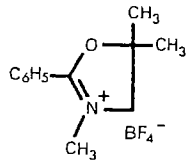


103 104 105

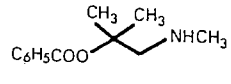
The reaction of hydroxide ion with imidate 106 should give the intermediate 107 in which stereoelectronic control promotes the cleavage of the C—N bond, while the 1,3-diaxial methyl-hydroxyl steric interaction favors the cleavage of the C—O bond. Hydrolysis of 106 gave exclusively the aminoester 108 (33); thus, stereoelectronic effects still control this reaction despite an important steric effect which favors the C—O bond cleavage. This result was also confirmed by the basic hydrolysis of imidate salt 109 which gave first the aminoester 110 which was then rapidly converted under the experimental conditions into the benzamidoalcohol 111.



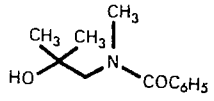
106 107 108



109

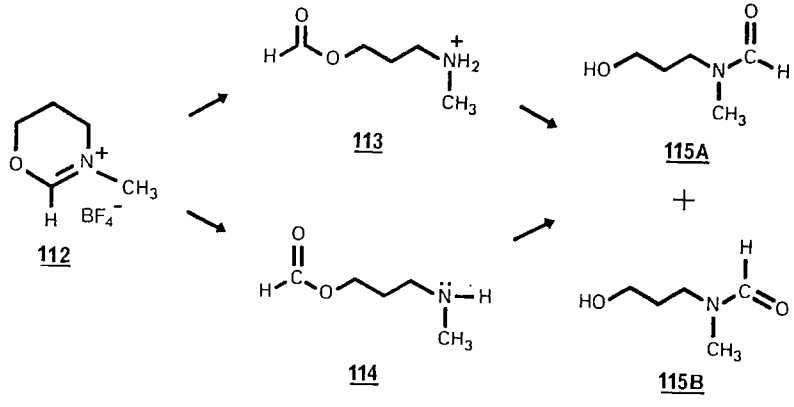


110



111

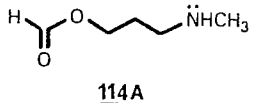
The acidic and basic hydrolysis of the cyclic imidate salt 112 was investigated (16). Under acidic conditions, imidate salt 112 was slowly hydrolyzed to yield the ester ammonium salt 113 exclusively. This is the expected result for any imidate salt.



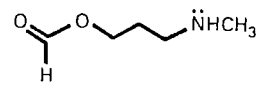
112 113 115A 114 115B

Under basic conditions, the hydrolysis of imidate salt 112 at 0°C gave a mixture (2:8) of the amidoalcohol rotamers 115A and 115B as the kinetic products of the reaction. Isomerization followed to yield the equilibrium ratio (4:6) of 115A and 115B. Imidate 112 is the first anti imidate salt which does not give the anticipated product, i.e. the aminoester 114. However, being a formate, thus a reactive ester, it is possible that under the reaction conditions, 114 recyclizes rapidly to give new tetrahedral intermediates which then yield a 2:8 mixture of amide rotamers 115A and 115B. This was proven by showing that the treatment of ester ammonium salt 113 under the same basic conditions at 0°C led directly to a 2:8 mixture of 115A and 115B.

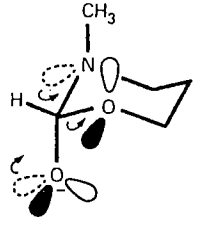
Being a formate ester, aminoester 114 must exist as a mixture of the Z and the E forms 114A and 114B where the Z form predominates. Cyclization of 114A and 114B with stereoelectronic control should give intermediates 116 and 117 which can then give the amide rotamers 115A and 115B respectively. The experimental results show that the formation of 115B is favored. The peculiar reactivity of imidate salt 112 is thus readily explained.



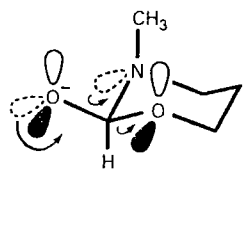
114A



114B



116

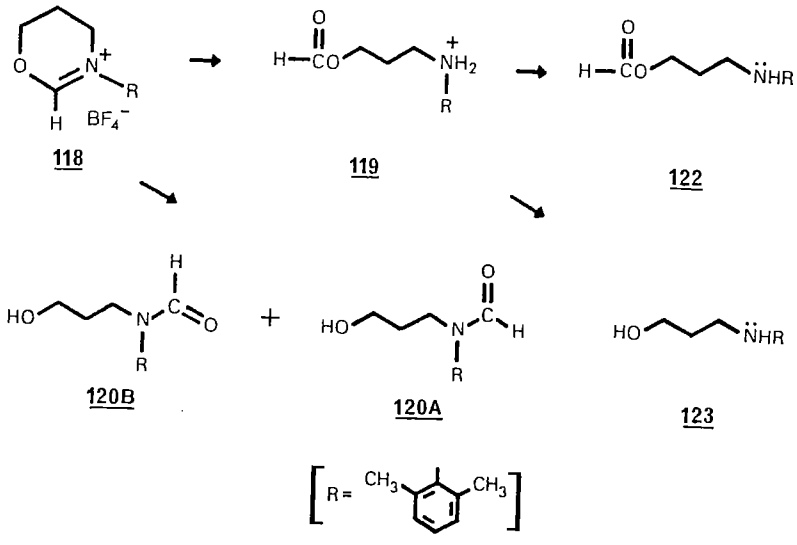


117

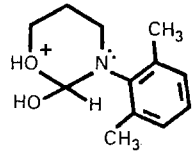
115A 115B

The hydrolysis of the cyclic imidate salt 118 was also studied (16). The imidate salt 118 (R=$(CH_3)_2C_6H_3$—) behaved in a completely different manner from the salt 112. Under acidic conditions, it yielded a ≈1:1 mixture of ester ammonium salt 119 and the amidoalcohol 120. Again, the hydrolysis is a slow process, and it could be observed (at the beginning of the reaction) that the amidoalcohol was first formed as the least stable rotamer 120B only. Rotamer 120B was then slowly isomerized to give an equilibrium mixture of 120A (67%) and 120B (33%).

The behavior of imidate 118 under acidic conditions can be readily explained by the presence of the two methyl groups on the phenyl ring which create an important steric hindrance to protonation of the nitrogen atom in the resulting tetrahedral intermediate. The salt 118 reacts with water to give first a tetrahedral intermediate in the neutral T° form. However, the conversion



of T° into the $T^{\pm}$ or T^{+} ionic form does not occur readily. So, the intermediate gives in part the ester ammonium salt 119 via T^{+} or $T^{\pm}$ and in part the amidoalcohol 120 via T° or more likely via T° protonated on the OR group as in 121. The specific production of rotamer 120B is discussed below.



The basic hydrolysis of imidate salt 118 takes a different course from that of imidate salt 112, yielding first only the amide rotamer 120B which is then slowly isomerized to the equilibrium mixture (ratio 3:1) of 120A and 120B. Treatment of the ester ammonium salt 119 under the same basic conditions gave directly the aminoalcohol 123. This result shows that the aminoester 122 is not an intermediate in the basic hydrolysis of imidate 118. The formation of the amide rotamer 120B is therefore the result of the direct fragmentation of a tetrahedral intermediate which is formed from 118.

The two methyl groups on the phenyl ring of imidate salt 118 are responsible for its different reactivity by comparison with the other anti imidate salts. These two groups create enough steric hindrance in the resulting tetrahedral intermediate that the tertiary nitrogen cannot be hydrogen-bonded with the solvent and the cleavage of the C — N bond is prohibited. Thus, the reaction of hydroxide ion on imidate 118 must give intermediate 124 (Fig. 8). Intermediate 124 cannot break down with stereoelectronic control to yield the amidoalcohol 120, and it cannot give the aminoester 122 because the nitrogen cannot form a hydrogen-bond with the solvent.

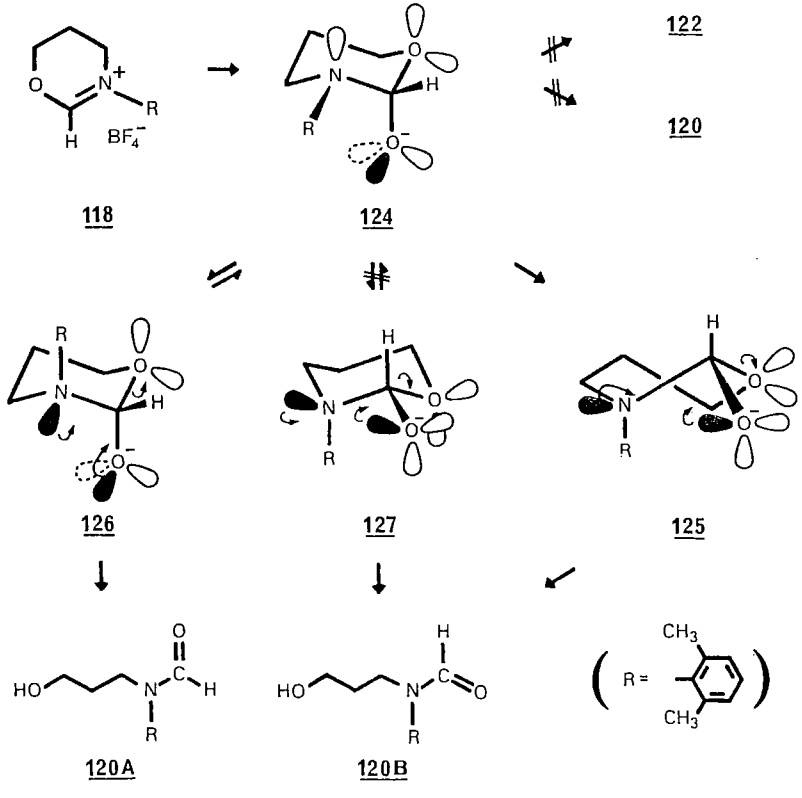
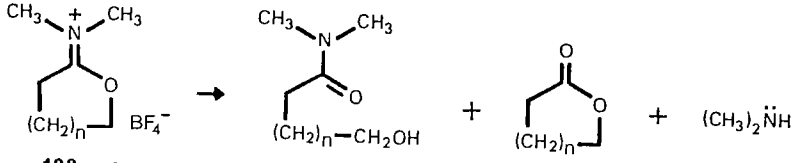


Fig. 8

Intermediate 124 will have to undergo a conformational change to cleave with stereoelectronic control. In 124, there is a very severe steric interaction between the hydroxyl and the 2,6-dimethylphenyl groups which can be lessened on going from 124 to the half boat 125. This steric interaction would be the main driving force for the specific conversion of 124 into 125 which has proper electron pair orientation to cleave the C – O bond and to produce exclusively the amide rotamer 120B. The half boat 125 would be formed in preference to intermediate 126 (via nitrogen inversion) or 127 (via a chair inversion) because these intermediates have the bulky R group on the nitrogen axially oriented. Note also that 126 and 127 lead to amide rotamers 120A and 120B respectively. The chair inversion process which leads to 127 with an axial R group cannot be a lower energy process than the nitrogen inversion which gives 126 also with an axial R group. Thus, because the amide rotamer 120B is the only product observed experimentally, intermediates 126 and 127 must be eliminated.

Imidate salts having a syn conformation were also studied (33). Imidate salt 128 which has a syn conformation due to its cyclic structure, gave on basic hydrolysis a mixture of amidoalcohol 129 (66%), δ-valerolactone (130, 33%) and dimethylamine (33%). Likewise, the hydrolysis of imidate salt 131 gave a one to one mixture of the corresponding amidoalcohol 132 and γ-butyrolactone 133 plus dimethylamine.

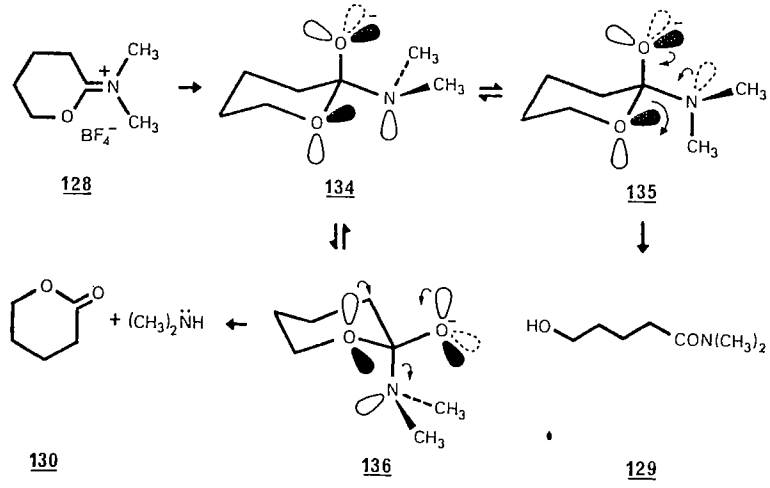


128 n = 2
131 n = 1

129 n = 2
132 n = 1

130 n = 2
133 n = 1

These syn salts give a mixture of products as predicted. Thus, for instance, the imidate salt 128 (Fig. 9) must react to produce first the intermediate 134 which cannot break down with stereoelectronic control. However, intermediate 134 can undergo a conformational change to give either 135 by carbon-nitrogen rotation (or inversion) or 136 by chair inversion. Intermediate 135 can only yield the amidoalcohol 129 whereas intermediate 136 can only give δ-valerolactone (130) and dimethylamine.



128 **134** **135**

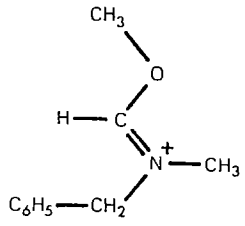
130 **136** **129**

Fig. 9

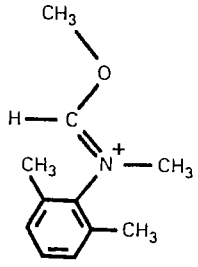
An interesting study (15) has been carried out with formamide derived imidate salts which have two different alkyl groups on the nitrogen atom. The unsymmetrical imidate 137 was obtained as a 3:1 mixture of isomers 137A and 137B and the imidate 138 as isomers 138A and 138B which were obtained pure on separation. It has already been mentioned that imidate salts derived from formamide exist in the syn conformation and that salt 138B has been analyzed by X-ray (cf. 52).

Hydrolysis of the mixture of the two isomers 137A and B under acidic conditions gave only the ester and amine products (methyl formate and the salt of N-benzyl-N-methylamine). The imidate salt 138A behaved differently yielding 70% of the amide and alcohol products (2,6-dimethylphenyl-N-methylformamide and methanol) with only 30% of the ester and amine products (methyl formate and the salt of N-methyl-2,6-dimethylaniline). The hydrolysis of 138A was repeated with ^{18}O enriched water and the resulting amide showed a complete incorporation of the labeled oxygen. This shows that the hydrolysis of 138A proceeds via the formation of a tetrahedral intermediate.

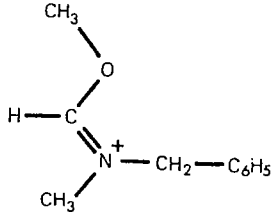
Consequently, the isomers 137A and 137B in acidic conditions gave the expected result. The difference in behavior of salt 138A can again be explained



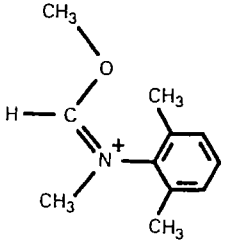
137A



138A



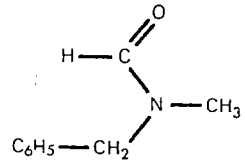
137B



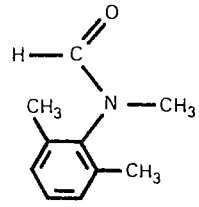
138B

by the presence of the two methyl groups on the phenyl ring which caused a severe steric hindrance to the protonation of the nitrogen in the tetrahedral intermediate. Thus salt 138A forms first a tetrahedral intermediate present as neutral T° which is then partly converted into the T^+ or $T^{\pm}$ ionic form to give the ester and amine products. The T° form is also partly protonated at the OR oxygen to give the amide and alcohol products.

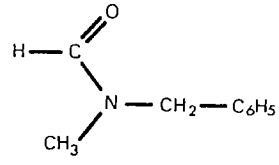
The results obtained under basic conditions are more interesting. Hydrolysis of the 3:1 mixture of 137A and B under basic conditions gave 25% of the ester and amine and 75% of the amide and alcohol products. Under these conditions the imidate salt 138A behaved differently giving 100% of the amide and alcohol products. An identical result was obtained with imidate salt 138B. It was further observed that in the case of 137A and 137B, the tertiary amide produced was an equilibrium mixture of the corresponding rotamers 139A (56%) and 139B (44%). In the hydrolysis of 138A or 138B, an equilibrium mixture of the amide rotamers 140A (77%) and 140B (23%) was also observed.



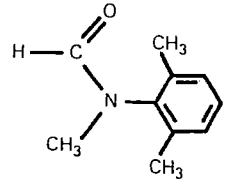
139A



140A



139B



140B

The difference in products observed from imidate salts 137A and 137B by comparison with imidate salts 138A and 138B can again be readily explained. Imidate salts 137A and 137B behave like typical syn imidate salts as they yield a mixture of ester and amine plus amide and alcohol products. In the case of imidate salts 138A and 138B, the formation of the ester and amine products is prohibited because the nitrogen atom in the tetrahedral intermediates cannot form a hydrogen bond with the solvent. The next task is to explain the formation of the equilibrium mixture of the amide rotamers 139A-B and 140A-B.

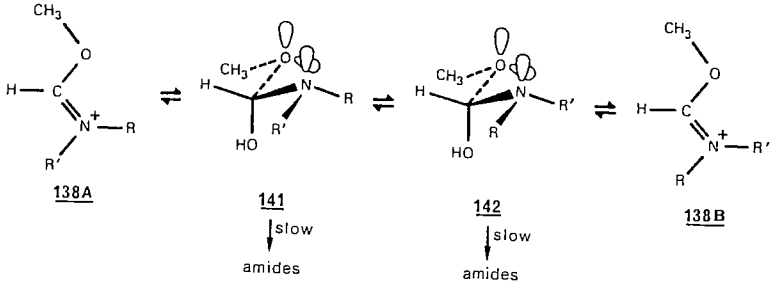
It should be pointed out (a) that the half-life of each rotamer in formamides 139 and 140 is several minutes at room temperature, (b) that the basic hydrolysis of the imidate salts 137 and 138 is completed in less than one minute at that temperature. Consequently, the production of the equilibrium mixture of the amides rotamers comes from the direct fragmentation of tetrahedral intermediates. It cannot come from a subsequent equilibration of the amide rotamers.

These results can be explained by postulating that the tetrahedral intermediates can freely rotate prior to the cleavage even if they can break down with stereoelectronic control. This postulate is supported by the important carbonyl-oxygen exchange observed in the course of the basic hydrolysis of

tertiary formamides. Indeed, this study showed clearly that in formamide derived tetrahedral intermediates, conformational changes can readily occur prior to the breakdown, even if the cleavages are allowed stereoelectronically.

Consequently, each unsymmetrical imidate salt must first produce a tetrahedral intermediate which has a specific conformation, then equilibration occurs to give a mixture of different tetrahedral conformers which can then break down to give the reaction products.

Strong evidence has been obtained that there is conformational change in these tetrahedral intermediates by carrying out the hydrolysis of imidate salts 138A and 138B in water (15). Under these conditions, the hydrolysis reaction is slow. It was observed that imidate 138A (or 138B) undergoes an isomerization to 138B (or to 138A), with which it reaches an equilibrium before the hydrolysis reaction is complete. This result shows that 138A reacts with water to form intermediate 141. Intermediate 141 can then equilibrate with intermediate 142 (by nitrogen inversion followed by a 180° rotation of the C – N bond). Intermediates 141 and 142 then give back 138A and 138B at a faster rate than their breakdown into the hydrolysis products.



The basic hydrolysis of these unsymmetrical formamide-derived imidate salts can therefore be rationalized in the following way. The unsymmetrical imidate 138A reacts with hydroxide ion to give first the intermediate 143 (Fig. 10). Similarly, its isomer 138B gives first the intermediate 144. Intermediates 143 and 144 cannot break down to the hydrolysis products with stereoelectronic control. Intermediate 143 can be converted into intermediate 145 via a C – N bond rotation and into 146 via a nitrogen inversion process. Intermediate 144 can also give intermediates 145 and 146. The intermediates 143-146 are therefore easily interconvertible and the cleavages occur through

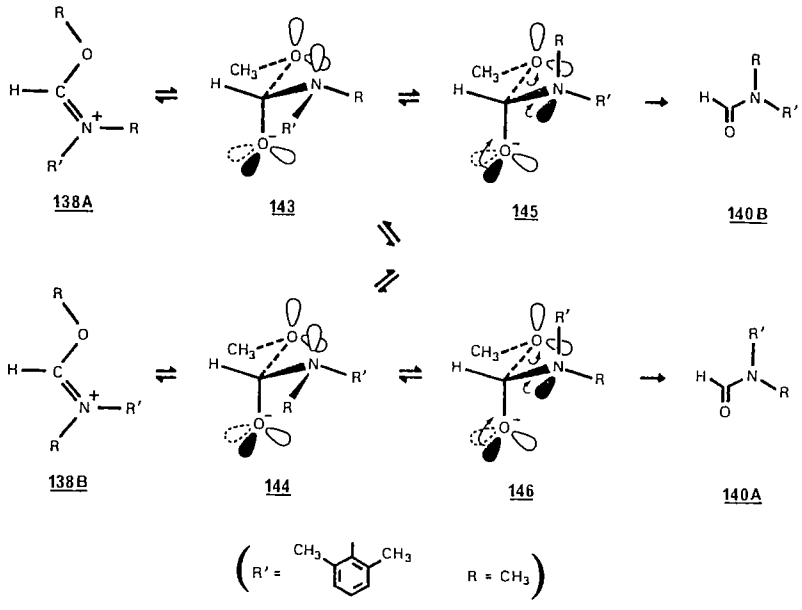


Fig. 10

145 and 146, yielding the amide rotamers 140B and 140A respectively. As a consequence, the conversions 145 → 140B and 146 → 140A are the determining steps of this hydrolysis reaction. Since an equilibrium mixture of the amide rotamers is produced, it means that the difference in energy between the two transition states involved in 145 → 140B and 146 → 140A are similar to that of the amide rotamers.

The relative stability of the rotamers 140A to 140B depends upon their difference in resonance energy and the relative steric repulsions which the oxygen and the hydrogen are experiencing with the two different R and R' groups. Thus, the relative populations of the two rotamers are directly related to their relative steric repulsions (35, 36).

The two electron pairs, one on the nitrogen and one on the oxygen (O^-), which are oriented antiperiplanar to the C – OR bond constitute the most important driving force which governs the cleavages 145 → 140B and 146 → 140A. However, in both cleavages, on going from the tetrahedral intermediate to

the amide, steric interactions increase. Therefore the discriminating factors in these cleavages are the steric effects of the R and R' groups relative to the oxygen and the hydrogen. On that basis, the energy difference between the two transition states 145 → 140B and 146 → 140A will be similar to the energy difference of the two rotamers. This also means that the geometry of the transition states must be close to that of the amide rotamers.

The direct formation of the equilibrium mixture of amide rotamers from the fragmentation of tetrahedral intermediates for imidate salts 138A and 138B is thus rationalized. The same explanation is also valid for the formation of the equilibrium mixture of the amide rotamers 139A and 139B from imidate salts 137A and 137B.

It is however interesting to point out that in the case of imidate salts 137A and 137B, the ester and amine products were also observed. Thus, in this particular case, C – N bond cleavage is able to compete with cleavage of the C – O bond (even though conformational change is allowed). It has already been mentioned that in tetrahedral conformers which can give either an amide or an ester in the Z conformation, the ejection of the amino group is favored by one additional secondary electronic effect. This might therefore be the explanation for the observed results with formamide derived imidate salts.

Imidate salt 138A was also found to be isomerized with 138B in the presence of methanol, but no further reactions took place (15). This is in contrast with the closely related imidate salt 147 (Fig. 11) which reacts with methanol to yield trimethylorthoformate and N-methyl aniline fluoroboric acid salt. The isomerization of imidate salts 138A and 138B takes place because a tetrahedral intermediate is formed by the reaction of methanol. Contrary to 147, the salts 138A and 138B do not undergo further reaction because the nitrogen in the resulting tetrahedral intermediate cannot be protonated.

The hydrolysis of the β-lactam derived imidates 148 and 151 was also reported (17). The results are described in Table 3. The results obtained with imidate 148 are those expected for an imidate existing in the syn or as a mixture of the syn and anti conformation. The difference in behavior of imidate 151 can again be explained by the presence of the bulky 2,6-dimethylphenyl group. In basic conditions, this group prohibits hydrogen bonding of the tertiary nitrogen and, consequently, the β-lactam 152 is formed exclusively. Under mild acid conditions, this bulky group prevents

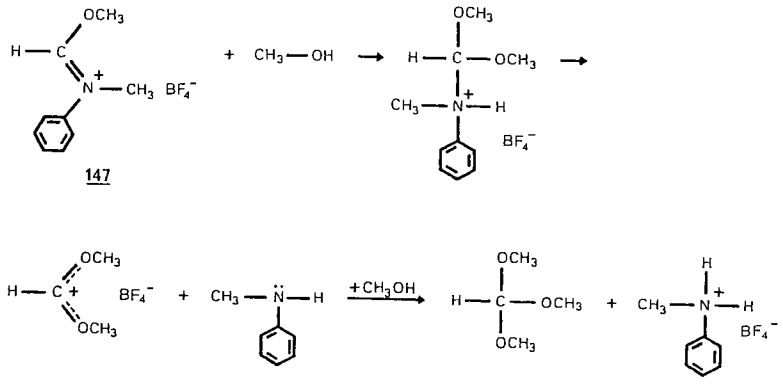
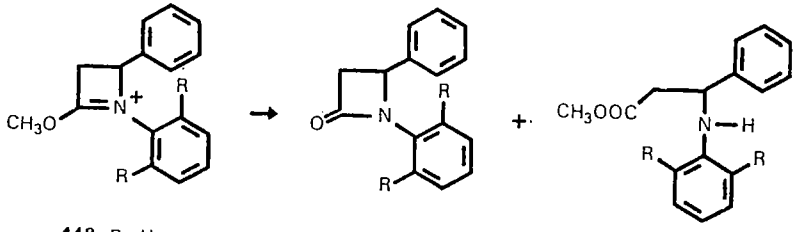


Fig. 11

TABLE 3 Hydrolysis of Imidate Salts 148 and 151 as a Function of pH at Room Temperature

medium	imidate salt 148		imidate salt 151	
	β-lactam 149 (%)	ester-amine 150 (%)	β-lactam 152 (%)	ester-amine 153 (%)
1.0 *N* NaOH	20	80	100	0
pH 12.7	12	88	100	0
pH 9	0	100	100	0
pH 7	0	100	100	0
pH 4	0	100	68	32
0.1 *N* HCl	0	100	56	44
0.5 *N* HCl	0	100	65	35
1.5 *N* HCl	0	100	87	13
3.0 *N* HCl	0	100	100	0
6.0 *N* HCl	0	100	100	0

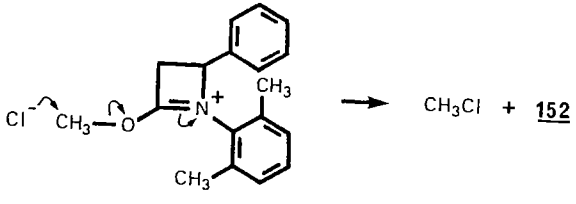
in part the protonation of the tertiary nitrogen, so a mixture of β-lactam 152 and aminoester 153 is produced. Interestingly, under increasingly acidic conditions, the formation of β-lactam 152 becomes the exclusive process. It was however demonstrated by using ^{18}O-labeling that the formation of β-lactam 152 under these strong acid conditions occurs by an SN_2 type displacement reaction on the methoxy group by chloride ion (cf. 154), and the formation of methyl chloride was observed experimentally.



148 R = H
151 R = CH_3

149 R = H
152 R = CH_3

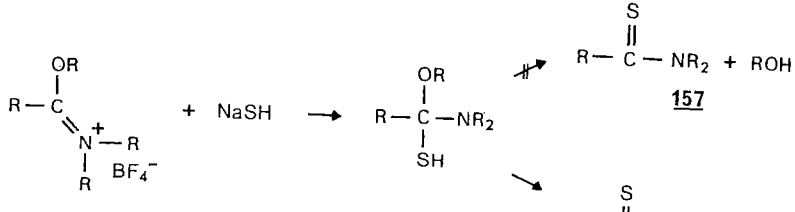
150 R = H
153 R = CH_3



154

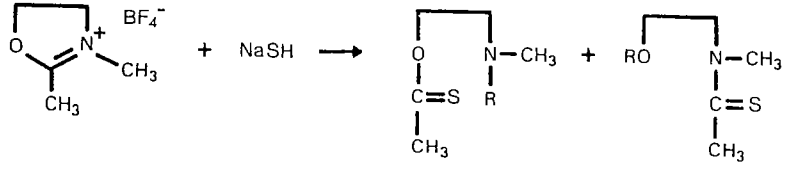
Cleavage of hemi-orthothioamide tetrahedral intermediates

Kaloustian and co-workers (37) have reported that the kinetic breakdown of hemi-orthothioamide tetrahedral intermediates (156) was found to involve the preferential cleavage of the C – N bond (→158) rather than the C – O bond (→157). The intermediate 156 were produced in situ by the reaction of sodium hydrosulfide on an imidate salt (155) in acetone.



155 **156** **157** **158**

Thin layer chromatography analysis (at room temperature) of the reaction mixture obtained from equimolar amounts of 2,N-dimethyl-1,3-oxazolinium fluoroborate (159) and sodium hydrosulfide at -78° gave the thioamidoalcohol 161A only. However, tlc analysis of a similar reaction mixture after low temperature trapping (AcCl/pyridine, -78°C) showed the thioester 160B as the major product along with the thioamide 161B (ratio ≈9:1).

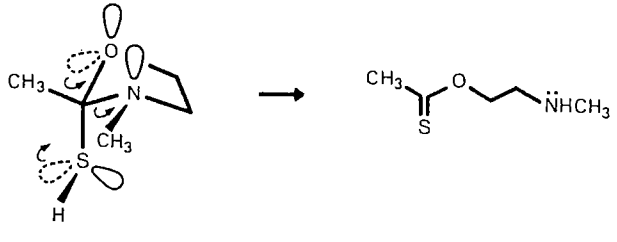


159

160A R = H
160B R = $COCH_3$

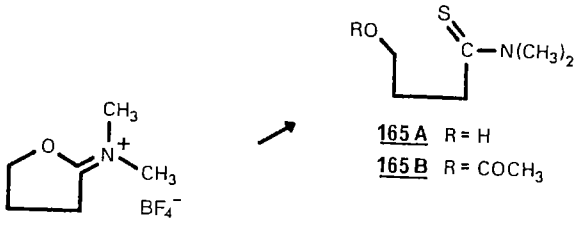
161A R = H
161B R = $COCH_3$

The reaction of hydrosulfide anion with the imidate salt 159 must give the tetrahedral conformer 162 which has an electron pair each on the nitrogen and the oxygen atoms oriented antiperiplanar to the C – SH bond. In 162, cleavage of the C – O bond is not allowed whereas the cleavage of the C – N bond can take place with primary and secondary (two secondary electronic effects) stereoelectronic control yielding 160A in the Z conformation 163.



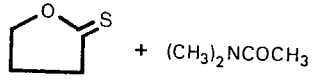
162 **163**

Analysis of the reaction mixture from equimolar amounts of anhydrous sodium hydrosulfide and N,N-dimethyliminobutyrolactonium fluoroborate (164) in acetone at room temperature revealed the thioamidoalcohol 165A only (32). However, when the reaction was run at -78°C, and the mixture acetylated (-78°C), the thionolactone 166 and N,N-dimethylacetamide (167) were the major detectable products.



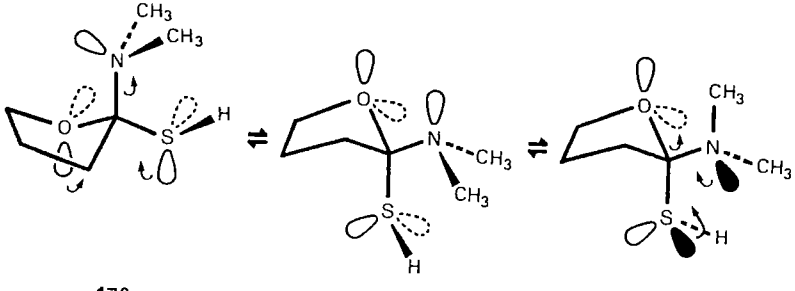
164

165A R = H
165B R = $COCH_3$



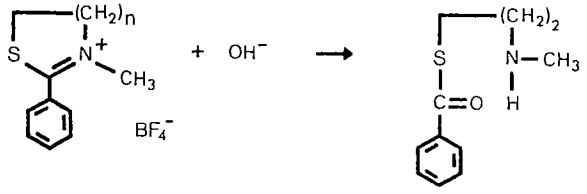
166 **167**

The stereoelectronically controlled reaction of hydrosulfide anion with imidate salt 164 must first yield the tetrahedral conformer 168. This intermediate cannot break down to yield either 165 or 166 and dimethylamine, but it can undergo a conformational change either at the nitrogen atom (↔169) or at the ring (↔170). Conformer 169 can only give the thioamidoalcohol 165A whereas conformer 170 can only produce the thionolactone 166 and dimethylamine. The experimental results indicate that the conformational change at the ring (↔170) is the preferred pathway at low temperature.



170 **168** **169**

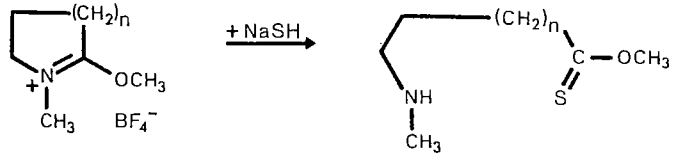
Khouri and Kaloustian (38) have recently observed that the hydrolysis of 2-phenyl-N-methyl-1,3-thiazolinium (171) and 2-phenyl-N-methyl-5,6-dihydro-1,3-thiazinium tetrafluoroborates (172) under kinetically controlled conditions (NaOH, 15-crown-5, anhydrous n-C_3H_7CN, Ac_2O, -78°C) proceed by preferential cleavage of the C—N bond (giving 173 and 174 respectively).



171 n = 1
172 n = 2

173 n = 1
174 n = 2

They have also observed that the sulfhydrolytic cleavage of O,N-dimethyl-butyrolactonium and O,N-dimethyl-valerolactonium tetrafluoroborates (175 and 176) involves C—N cleavage (giving 177 and 178 respectively), under kinetic control (61°C, NaSH, Ac_2O, $CHCl_3$) (39). These results can again be rationalized in terms of the principle of stereoelectronic control.



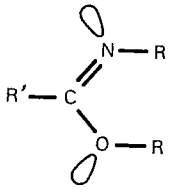
175 n = 1
176 n = 2

177 n = 1
178 n = 2

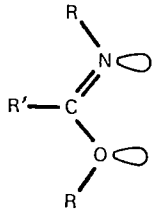
Imino-ethers, amidines, etc.

Imino-ethers can adopt theoretically the four conformations 179-182. In addition to the primary electronic effect, conformer 179 possesses two secondary electronic effects, conformers 180 and 181 only one whereas conformer 182 has none. Conformer 179 has a strong steric interaction between the two R groups and must be eliminated. Imino-ethers must therefore exist either in conformation 180 and 181. Meese, Walter, and Berger (40) have shown that the most stable conformation is 180. In some compounds where there is an important steric effect between the R' and the RN group, conformation 181 is also observed. It was also found that in a polar solvent (CH_3OH), there is a mixture of a major (180) and a minor (181) conformer.

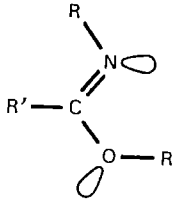
These results suggest that the secondary electronic effect caused by the electron pair of the oxygen atom in 180 is more important (cf. 183) than that of the nitrogen electron pair in 181 (cf. 184).



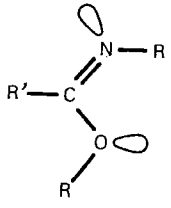
179



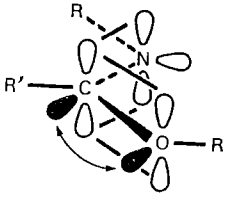
182



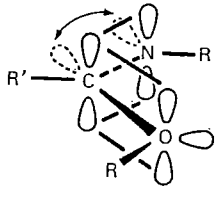
180



181

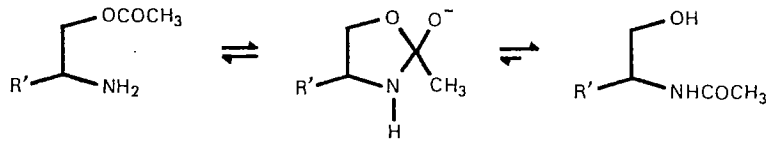


183

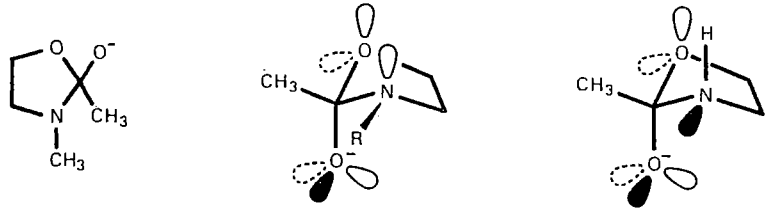


184

In a study on the aminolysis of O-acetylethanolamine (185, R'=H) and O-acetylserine (185, R'=COOH), it was observed (41) that the kinetics of acetyl-transfer reaction of these two aminoesters indicate that the breakdown of 186 yields mainly the amidoalcohol 187; only 1.5-3% of aminoester 185 was detected. The breakdown of 186 was compared with that of 188 obtained from imidate 94 (cf. p. 130) which gave only the aminoester 95 by C—N bond cleavage. Contrary to the conclusion reached by these authors (41), the difference in behavior between 186 and 188 can be readily understood. Imidate salt 94 reacts with hydroxide ion to give conformer 189 (R=CH_3) which can only give the aminoester 95 with stereoelectronic control; the amino-



185 186 187

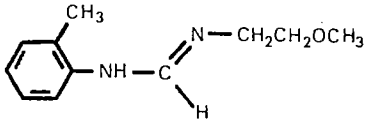


188 189 190

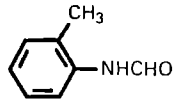
ester 185 can either form 189 (R=H) or 190. The interconversion of 189 (R=H) and 190 involves only a proton transfer which is a low energy process (cf. p. 109); thus, 190 (or 189, R=H) can give either the amidoalcohol or the aminoester product with stereoelectronic control. The experimental results show that the formation of the amidoalcohol product is favored.

The hydrolyses of a series of cyclic and acyclic amidines have been carried out by Burdick, Benkovic, and Benkovic (42) in order to assess the possible importance of stereoelectronic control of the ensuing tetrahedral intermediates.

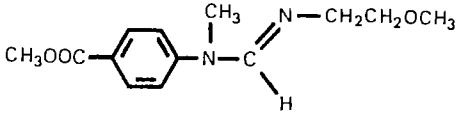
The acyclic amidines 191 and 192 gave only the corresponding kinetic products, i.e., formamides 193 and 194 respectively. The basic hydrolysis of the 7-membered amidine 195 gave only the thermodynamic product 196. However, on partial hydrolysis, 195 gave a mixture of the thermodynamic product 196 and the kinetic product 197. The six-membered amidines 198 and 199 yielded only the thermodynamic products 200 and 201. Attempts to observe the kinetic products 202 and 203 during partial hydrolysis failed. It was further observed that the basic hydrolysis of the trifluoroacetamide derivatives 204 and 205, two precursors of the kinetic products 202 and 203, yielded directly the thermodynamic products 200 and 201.



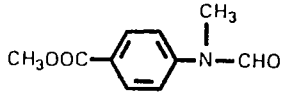
191



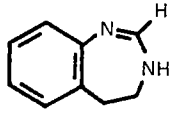
193



192



194



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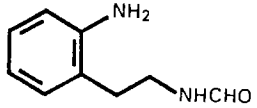
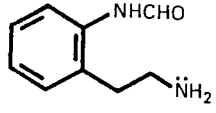


196



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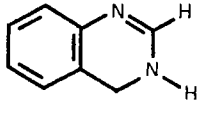

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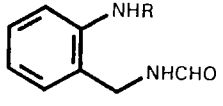
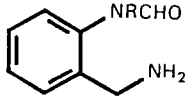
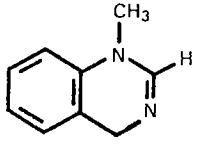


200 R = H
201 R = CH_3



202 R = H
203 R = CH_3



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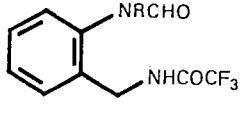
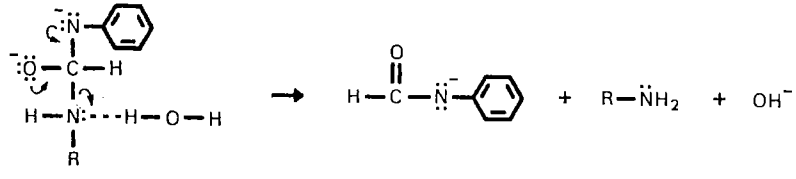


204 R = H
205 R = CH_3

Thus, the hydrolysis of 191 and 192 takes place under kinetically controlled conditions. There is evidence that 195 gave first the kinetic product 197 which would then be rapidly converted into the thermodynamic product 196. The hydrolysis of 198 and 199 occurs under thermodynamic control conditions to give 200 and 201 respectively. It is possible that 198 and 199 produced first the kinetic products 202 and 203 which would then be converted very rapidly into the thermodynamic products.

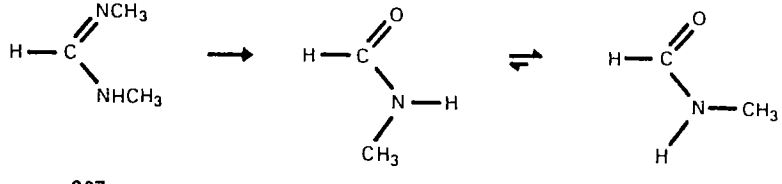
It does not seem possible to explain these results on the basis of the principle of stereoelectronic control alone. It is, however, interesting to notice that the ejection of the more basic nitrogen is favored in the kinetically controlled proces (43-45).

This may be due to the following: (a) the more basic nitrogen atom can form a stronger hydrogen bond with the solvent than the aniline nitrogen and (b) the hydrogen on the aniline nitrogen is acidic and can therefore be removed (or partly) under basic conditions. This would give transition state 206 which favors the cleavage of the more basic nitrogen.



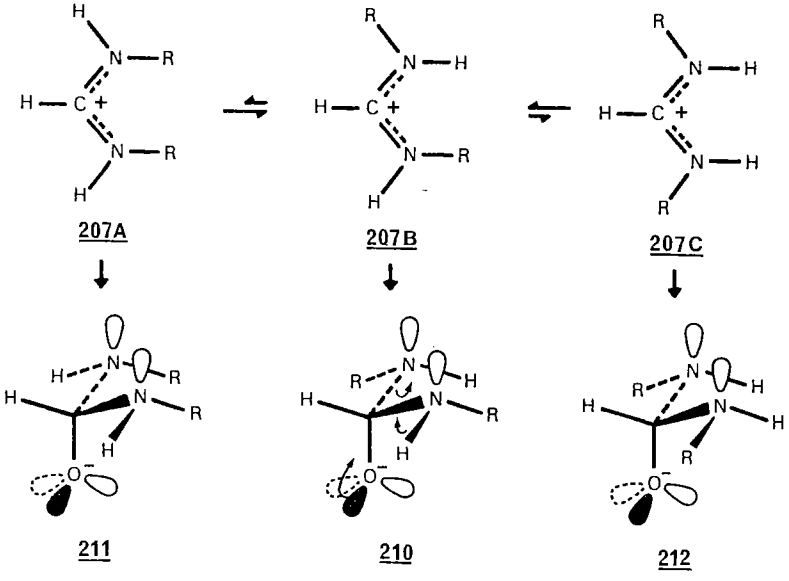
206

Halliday and Symons have reported (46) that the basic hydrolysis of N,N'-dimethylformamidine (207) yields the anti form 208 of N-methylformamide which is then isomerized into the most stable syn form 209.



207 208 209

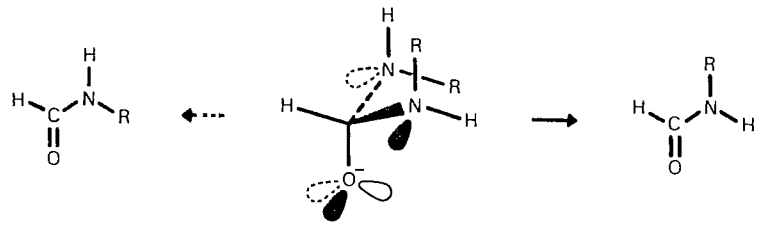
^{1}H nmr analysis showed that monoprotonated dimethylformamidine is present mostly as isomer 207B, with about 5% of 207C and no detectable 207A. The reaction of hydroxide ion with 207B should give conformer 210 which after appropriate proton transfer can only give syn-amide 209 with stereoelectronic control if conformational change at the nitrogen in 210 is not allowed. The same conclusion is reached with 207A (cf. 211). Furthermore, 207C gives a tetrahedral intermediate (212) which cannot break down with stereoelectronic control.



207A 207B 207C

211 210 212

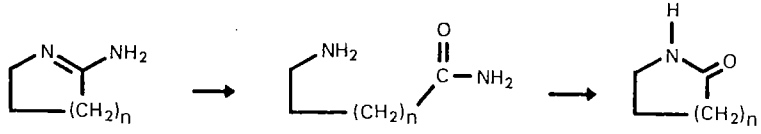
It is therefore not possible to form the anti-amide 208 unless conformational changes at the nitrogen are allowed. It is however reasonable to make such an assumption for formamide-derived tetrahedral intermediates (cf. p. 112). We can therefore analyze the cleavage of a tetrahedral conformer such as 213. This conformer can either give the anti or the syn-amide isomers (208 and 209) with stereoelectronic control. It is however not clear on that basis, why the formation of the less stable anti form 208 is favored. There must be another parameter in this case which is not known yet.



209 213 208

Recent developments

Perrin and Arrhenius (47) have studied the basic hydrolysis of cyclic amidines 214 and 215. They found that the primary product of hydrolysis of 214 (or 215) is solely the aminoamide 216 (or 217), and the lactam 218 (or 219) is a secondary product which is formed from the corresponding aminoamide.



214 n = 2
215 n = 1

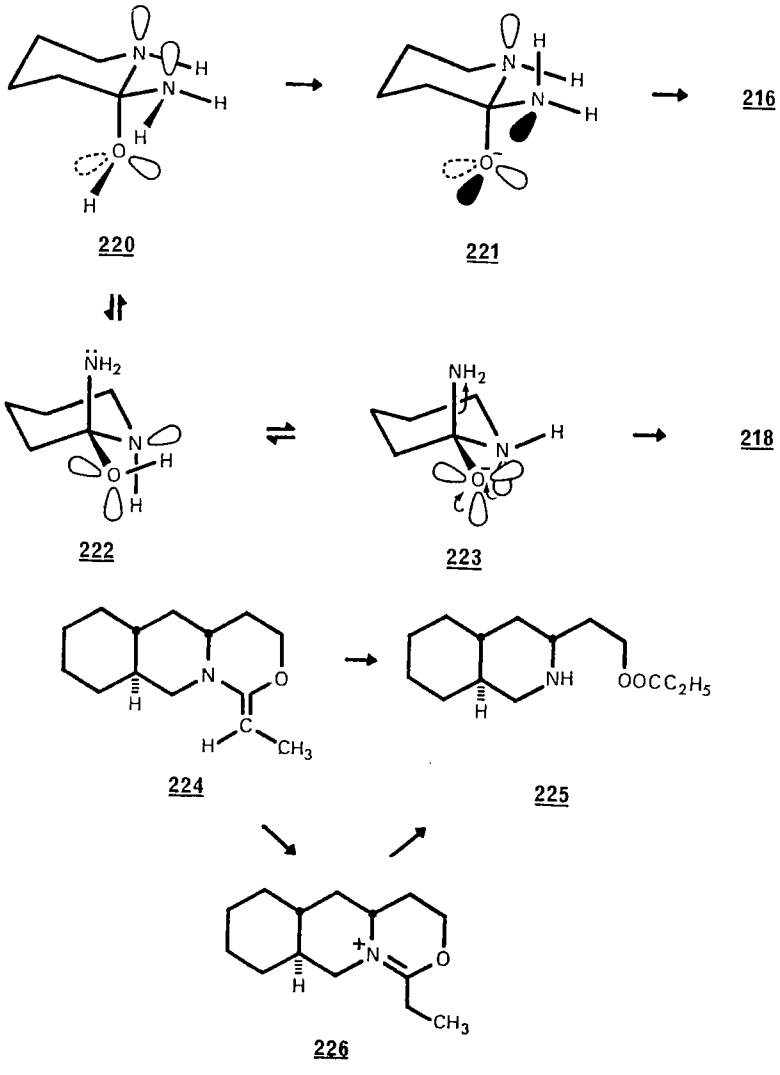
216
217

218
219

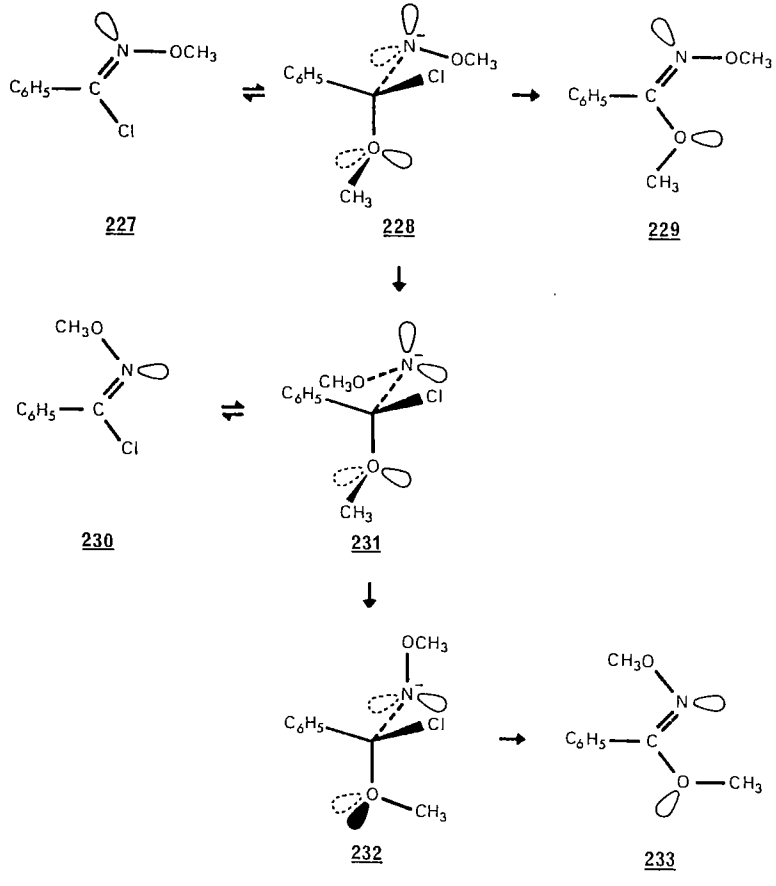
These results can be readily explained. For instance, the reaction of cyclic amidine 214 with hydroxide ion in water must give first the tetrahedral intermediate 220, which after appropriate proton transfer (→221) can only give the aminoamide 216 with stereoelectronic control. In order to form the lactam 218, intermediate 220 must undergo a conformational change to intermediate 222 followed by an appropriate proton transfer (→223). Since lactam 218 is not observed under kinetically controlled conditions, the conformational change 220 ⇌ 222 cannot compete with the breakdown of 220 via 221. Lactam 218 is then slowly formed from aminoamide 216 via intermediate 222.

Recently, Eschenmoser, Dunitz, and co-workers (48) have reported the hydrolysis of tricyclic ketene N,O-acetal 224 which yields only aminopropionic acid ester 225. The first step in this reaction must be the protonation of 224 which gives the anti imidate salt 226. Since anti imidate salts always

yield the aminoester under kinetically controlled conditions (cf. p. 124), the above result is readily explained. A similar case was observed by Meyers and Nazarenko (49).



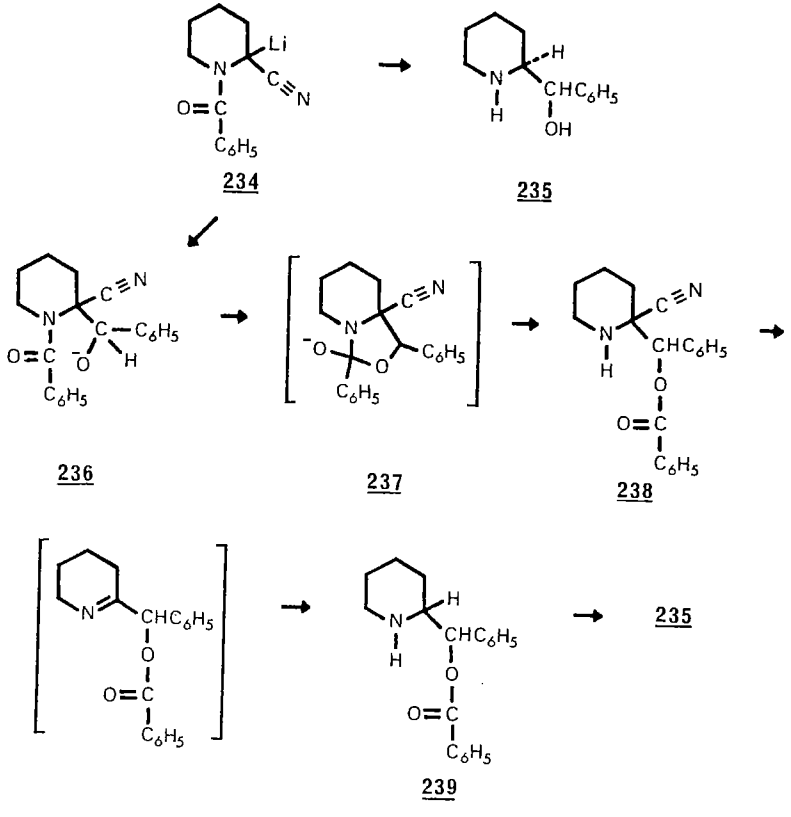
Johnson, Nalley, Weidig, and Arfan (50) have investigated the stereochemistry of the reaction of sodium methoxide with the isomeric O-alkylbenzohydroximoyl chloride 227 and 230 in dimethylsulfoxide-methanol (9:1). They found that 227 gave almost exclusively the Z-isomer 229 while 230 gave a mixture of Z and E isomers 229 and 233 where the E isomer largely predominates.



The authors have rationalized their results on the basis of the principle of stereoelectronic control. The reaction of methoxide ion on 227 gives the intermediate 228 which can eject chloride ion to give the Z isomer 229. The

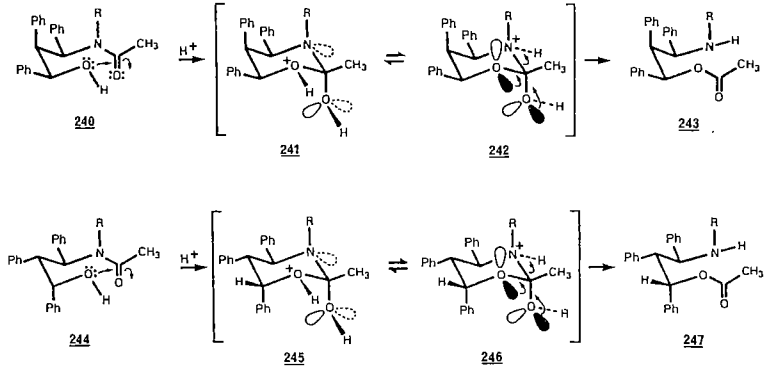
reaction of methoxide ion on 230 gives the intermediate 231 which cannot undergo a stereoelectronically controlled ejection of chloride ion. Thus, intermediate 231 would undergo a stereomutation to intermediates 228 and 232. Intermediate 232 can eject chloride ion to give the E isomer 233 and this process would predominate over the process 231 → 228 → 229.

Stork, Jacobson, and Levitz (51) have recently reported that the reaction of the lithium carbanion 234 with benzaldehyde followed by reduction with sodium borohydride gave the phenylcarbinol 235. The sequence of events in the transformation of 234 to 235 was shown to be as depicted below. Convincing spectral evidence was obtained for 236, 238, and 239. Thus, the hemiorthoamide tetrahedral intermediate 237 which was generated in situ gave the aminobenzoate 238, the expected product from stereoelectronic control.



Lyapova, Pojarlieff, and Kurtev (52) have studied the N → O and O → N acyl migration in 1-amino-1,2,3-triphenylpropanols under acidic and basic conditions respectively. They found a great difference in the ease of migration which depends on the relative stereochemistry of the substrate and the degree of substitution of the nitrogen atom (NH or NCH_3).

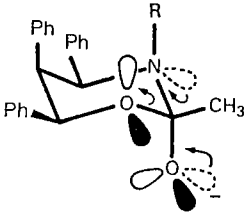
Under acidic conditions (0.58 M HCl in dioxan:THF (1:1) at 50° for 24 h), the isomeric acetamidoalcohols 240 and 244 are converted into the ammonium salts of the isomeric aminoesters 243 and 247 respectively. These N → O acyl migrations take place via the intermediates 241, 242, and 245, 246 respectively. Interestingly, they found that when R=H, the conversion 240 → 243 takes place readily but when $R=CH_3$, no reaction was observed. On the other hand, the conversions 224 → 247 ($R=CH_3$ or H) are both sluggish.



These results can be readily interpreted if the rate-determining step of these reactions is the formation of the tetrahedral intermediates 241 and 245. Indeed, there is a direct relationship between the relative ease of formation of these two intermediates (which depends upon their respective steric hindrance) and that of the acetamidoalcohol products 243 and 247 (R=H or CH_3). In intermediate 241, when $R=CH_3$, there is a strong 1,3-diaxial steric interaction between the N–CH_3 group and the axial phenyl group. Such steric interaction does not exist when R=H. Consequently, the formation of acetamidoalcohol 243 (via 241) should occur with ease only when R=H. This conclusion agrees with the experimental results. In the case of intermediate 245, when $R=CH_3$, there is no 1,3-diaxial steric interaction caused by the N-methyl group. On that basis, intermediate 245 ($R=CH_3$) should be readily formed. However in this intermediate, there is a strong 1,3-diaxial steric

interaction between the phenyl group at C-6 and the OH group. So, the formation of acetamidoalcohol 247 (via 245) must be equally difficult when R=H or CH_3. This is again in accord with the experimental results.

The authors have also observed that under basic conditions (0.02 M - Na_2CO_3 in aqueous acetonitrile) the process 243 → 240 is fast when R=H but slow when R=CH_3. On the other hand, the process 247 → 244 is relatively slow (15 min when R=H and 120 min when R=CH_3). Under basic conditions, these migration reactions must take place via the T^- tetrahedral intermediates 248 and 249 respectively. Again, if the formation of these two intermediates is the slow step, these results can be readily interpreted. Indeed, there is a strong 1,3-diaxial steric interaction in intermediates 248 (R=CH_3) and 249 (R=H or CH_3), so only intermediate 248 (R=H) should be readily formed.



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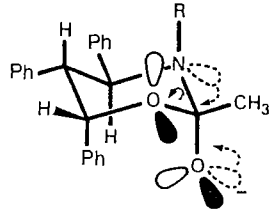
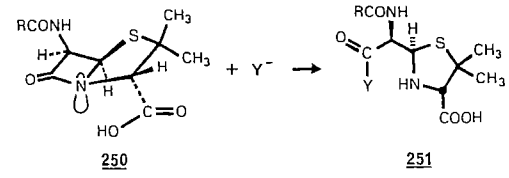


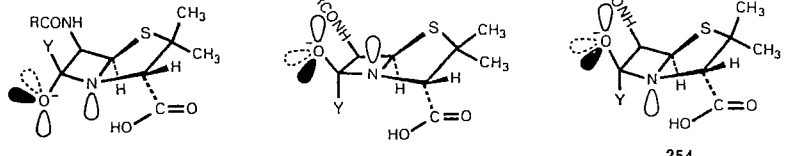
249

Finally, it should be pointed out that the stereochemistry of the tetrahedral intermediates 241, 245, 248, and 249 can only be obtained by application of the principle of stereoelectronic control in hydrolytic processes. The above results must therefore be accepted as strong evidence in favor of the validity of this principle.

Penicillin is a V-shaped molecule which has a fairly rigid structure due to the fusion of the β-lactam and the thiazolidine rings. As a consequence, the electron density of the β-lactam nitrogen lone pair should be concentrated heavily on the α-face of the penicillin molecule (cf. 250), and the β-lactam nitrogen cannot adopt the sp^2 hybridization found in normal amides; the conjugation between the nitrogen lone pair and the carbonyl group is thus reduced. This effect (53) in addition to the strain of the β-lactam ring (54), activates the carbonyl lactam function and the great susceptibility of penicillin to react with nucleophiles (250 → 251) is thus readily understood.

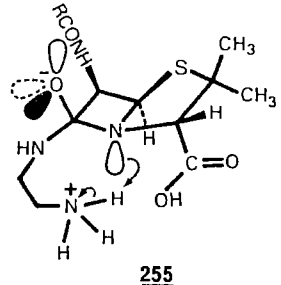


250 251



252 253 254

According to the theory of stereoelectronic control, the direction of nucleophilic attack on the lactam carbonyl carbon is such that the lone pairs on the heteroatoms will be antiperiplanar to the attacking group. Nucleophilic attack on penicillin should therefore take place preferentially from the β-side (cf. 252) rather than the α-side (cf. 253) as the former gives a tetrahedral intermediate which has a cis rather than a trans ring junction. Indeed, the cis intermediate 252 is much less strained than the trans intermediate 253. However, the β-face of penicillin is sterically hindered and Page and collaborators (55-59) have suggested that the nucleophilic attack would take place from the least hindered α-side yielding directly the tetrahedral conformer 254, in disagreement with the prediction of the theory of stereoelectronic control. This suggestion was made because in the course of the kinetic studies on the aminolysis and the hydrolysis of penicillins (55-57), it was found that the reaction of 1,2-diaminoethane



255

monocation with benzylpenicillin shows a rate enhancement of 100-fold compared with a monoamine of similar basicity. This rate enhancement was attributed to an internal proton transfer (intramolecular general acid catalysis) from the primary ammonium group to the tertiary nitrogen which can occur from intermediate 255, implying that nucleophilic attack must take place from the least hindered α-side of penicillin!

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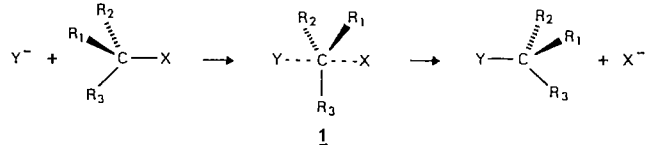
CHAPTER 5

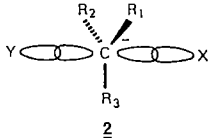
REACTIONS AT SATURATED CARBONS

SN_2 type reaction

The concerted displacement of a leaving group by a nucleophile in aliphatic and alicyclic compounds, i.e. the SN_2 reaction, is one of the first reactions which was found to take place with stereoelectronic control (1, 2). This reaction is a one step process without intermediate resulting in a Walden inversion. The nucleophile must approach the substrate from a 180° angle opposite to the leaving group. The stereochemistry of the resulting transition state corresponds 1 where the central carbon can be considered to be, in molecular orbital terms, sp^2 hybridized. The remaining p-orbital has one lobe overlapping with the nucleophile and the other with the leaving group (cf. 2). The mechanism of this reaction is therefore controlled by electronic effects which impose a specific stereochemistry at the transition state level.



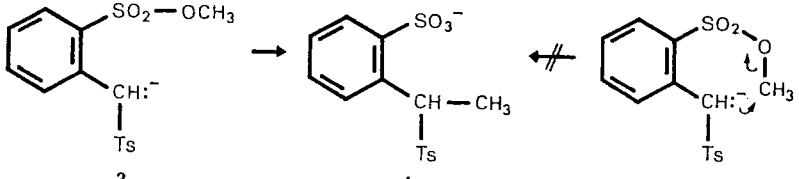
1



2

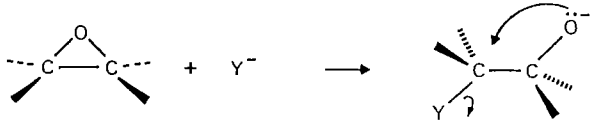
It is not easy to design an experiment to test the subtle stereochemical requirement of the transition state of a reaction. One experimental approach is to attach the nucleophile to the substrate, creating a situation where this nucleophile can undergo two different competing reactions. In many cases, the nucleophile can more easily fulfill the stereochemical requirement of one process and only one reaction is observed. The experiment is almost perfectly designed when the process which takes place is "stereoelectronically allowed" and leads to the kinetic rather than the thermodynamic product, or when the process which does not take place is not "stereoelectronically allowed" but is otherwise favored on the basis of steric arguments or entropy consideration, especially when that would have led to the thermodynamic product.

Using this approach, Eschenmoser and co-workers (3) have provided strong evidence that, in the SN_2 transition state, the nucleophile is aligned colinearly. They found that the anion 3 gave the expected product 4 via an intermolecular process rather than the "formally appealing" intramolecular process. The logical conclusion of this experiment is that the intramolecular attack (cf. 5) although entropically the most favored path, does not occur because the proper alignment of the nucleophile with the substrate cannot be attained in the transition state. This work represents also a beautiful example of an experiment designed to investigate the importance of stereochemistry in the transition state of an organic reaction.



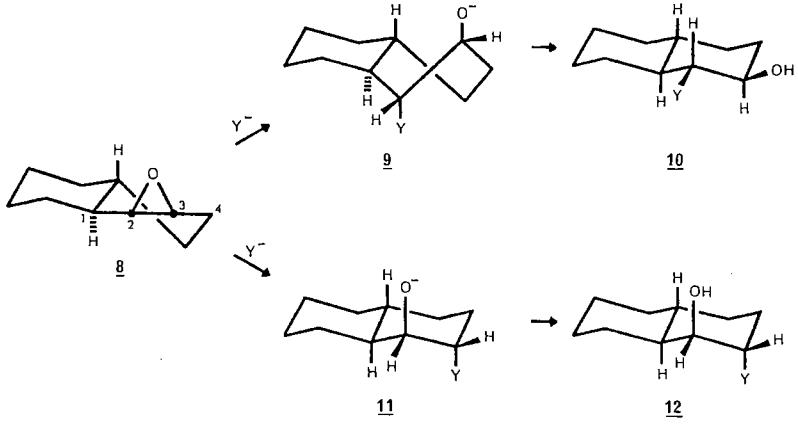
3 4 5

As a consequence of this stereoelectronic requirement, the opening of a symmetrical epoxide (6) by a nucleophile gives a product of defined stereochemistry (cf. 7). The same requirement necessarily holds for the reverse process, i.e. 7 → 6. Indeed, the formation of an epoxide from 7 can be regarded as an internal SN_2 reaction (footnote 20 in ref. 4, see also 5).



6 7

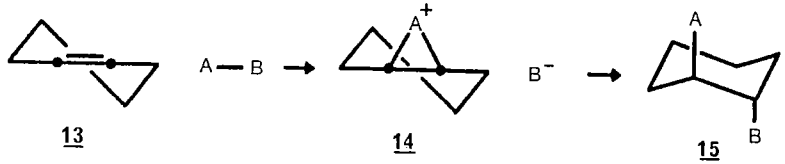
In the case of an unsymmetrical epoxide which is conformationally rigid such as 8, two different products are theoretically possible, the diequatorial product 10 resulting from the attack at C-2 or the diaxial product 12 from the attack at C-3.



8 9 10 11 12

As discussed by Valls and Toromanoff in 1971 (6), the electronically controlled stereochemistry of the transition state in the SN_2 reaction requires that the reaction at C-2 must give the twist-boat intermediate 9 which then gives compound 10 after a conformational change whereas the reaction at C-3 gives the chair intermediate 11 and thence 12. The formation of the transition state to produce 11 is a lower energy process than that leading to 9. Product 12 is thus formed in preference to 10 under kinetically controlled conditions. Indeed, it is well known that the epoxide opening gives the trans-diaxial product.

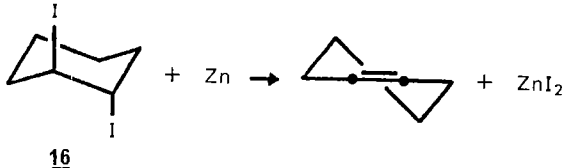
Most addition reactions of electrophilic reagents to double-bonds which are known to proceed through an epoxide-like intermediate (i.e. the three-membered ring intermediate 14), and, therefore, must follow the same principle, yielding the trans-diaxial product 15 (7).



13 14 15

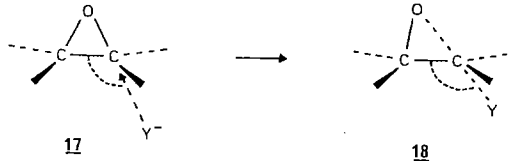
This is true for the addition of hydrogen halide (H−X), halogens (X−X) and other electrophilic reagents (NO − Cl, I − N_3, etc.) to cyclohexenes. The oxymercuration reaction ($Hg(OAc)_2$) in the presence of several nucleophiles (H_2O, AcOH, ROH) is another well known example.

The reverse process, i.e. 15 → 14 → 13, which is a method to produce olefins, takes place also with the same stereochemical requirements. The familiar reaction of a diaxial diiodo compound 16 with zinc illustrates the principle.



16

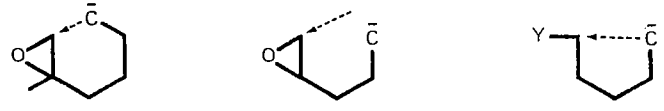
Following these general examples, we can now analyze the opening of epoxides in more detail. The size of the ring imposes geometric constraint and the SN_2 reaction demands colinearity. The approach of the nucleophile should then resemble 17 → 18, which is different from that in displacement of a leaving group on an aliphatic chain, i.e. 19 → 20.



17 18

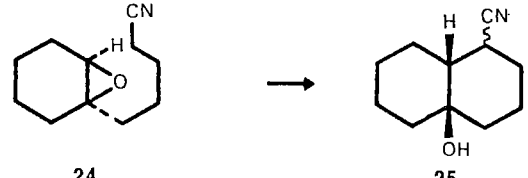
19 20

It is on the basis of this theoretical analysis that Stork deduced that the intramolecular opening of an epoxide yielding a six-membered ring should be more facile than that leading to a five-membered ring. Indeed, in the case of six-membered ring formation (21), the nucleophile is perfectly aligned for a backside colinear displacement whereas, in the five-membered ring formation (22), the positioning of the carbanion along the dotted line representing colinear approach requires considerable bond distortion. It should be pointed out that when the process leading to a five-membered ring involes a displacement as illustrated by 23, there is no particular constraint in locating the carbanion in the proper position for backside colinear displacement. Reactions of this type generally lead to faster formation of the five rather than the six-membered ring.

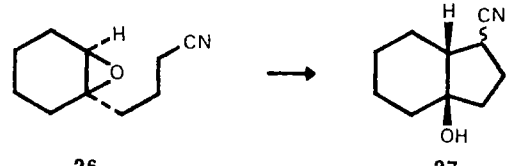


21 22 23

Experimental evidence in support of this was provided by Stork, Cama, and Coulson (8) who studied the cyclization under basic conditions (KNH_2, NH_3-DME) of epoxynitriles 24 and 26. They observed that the formation of the cyclohexane ring (24 → 25) was indeed easier than that of the cyclopentane ring (26 → 27).

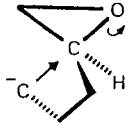


24 25



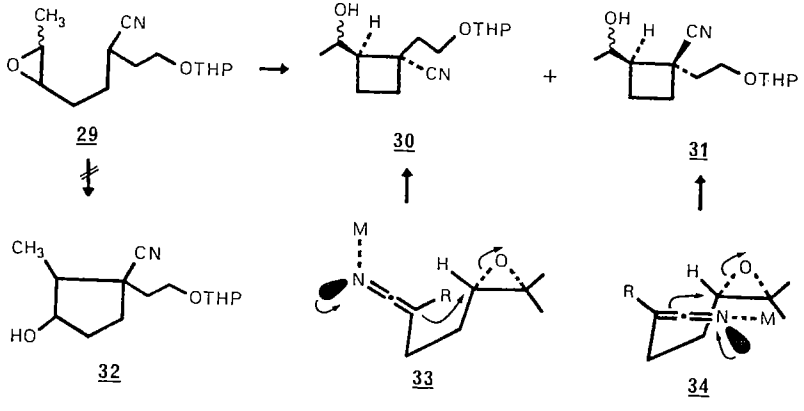
26 27

Stork then analyzed the transition state requirements for the formation of a four-membered ring (28) and realized that it seemed easier to attain collinearity in this case than in that of the five-membered ring (22), arriving at the unexpected conclusion that the former process could prevail over the latter.



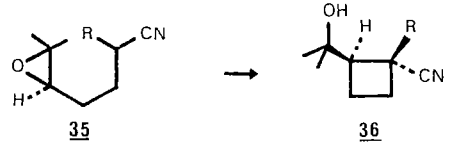
28

Stork and Cohen (9) have then found experimentally that indeed the cyclization of epoxynitrile 29 with lithium bis(trimethylsilyl)amide in benzene gave a 95:5 mixture of the isomeric cyano-hydroxy-cyclobutanes 30 and 31. Thus, with equal substitution at both ends of the oxirane ring, a cyclobutane is formed in preference to a cyclopentane ring (32). Note also that the major isomer 30 is the less stable isomer (two larger groups cis to each other). This shows that formation of transition state 33 leading to 30 is of lower energy than that of transition state 34 which gives 31. This new methodology of cyclobutane formation was used to synthesize (±)-grandisol starting from 30.



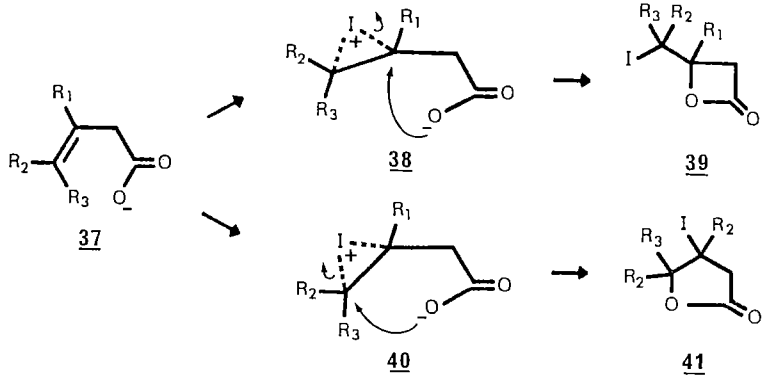
29 30 31 32 33 34

Obviously, when the oxirane carbon further from the nitrile is more substituted, the formation of a cyclobutane ring is even more favored since it involves a displacement at the less substituted end of the epoxide. Accordingly, cyanoepoxides 35 (R=H or CH_3) gave the cyclobutanes 36 (R=H or CH_3) (8). Note again that the specific formation of 36 ($R=CH_3$) shows that the preferred transition state is 33, not 34. This indicates that the effective steric hindrance of the cyano anion is in fact larger than that of a normal alkyl group as a consequence of the allenic structure of the metal salt. It is interesting to point out that the proposed geometrical requirement for the nitrogen electron pair, i.e. antiperiplanar to the π system of the double-bond which will eventually open the oxirane ring (see arrows in 33), is deduced from stereoelectronic principles (for more recent work on this topic see refs. 10 and 11).



35 36

Barnett and Sohn (12, 13, see also 14) have discovered that the iodolactonization of β,γ-unsaturated carboxylic acid salts 37 yield, under kinetically controlled conditions, the γ-iodo-β-lactones 39 in preference to the more stable β-iodo-γ-lactones 41. Similar results were obtained in the course of the bromolactonization reaction. Thus, here again, the formation of a four-membered ring is more facile than that of a five-membered ring. This can be rationalized on the basis of Stork's analysis, i.e. the internal opening by the carboxylate anion of the three-membered ring iodonium ion (or bromonium) 38 → 39 is preferred over the other mode of opening 40 → 41 for stereoelectronic reason.



37 38 39 40 41

Returning to internal opening of cyanoepoxides, the rate of cyclopropane formation (42) is such that this ring is produced in preference to a cyclobutane (43) regardless of the relative degree of substitution of the oxirane ring. For instance, cyclization of epoxynitrile 44 gave the cyanopropane 45 (9). It is well known that cyclopropanes are normally more readily formed than cyclobutanes; the internal opening of cyanoepoxides is therefore no exception. This suggests that, presumably through the use of "bent bonds", the nucleophilic alignment is better in 42 than in 43. In that case, cyclopropane would correspond to the bent-bond model of Coulson and Moffitt (15, see also 16).

42

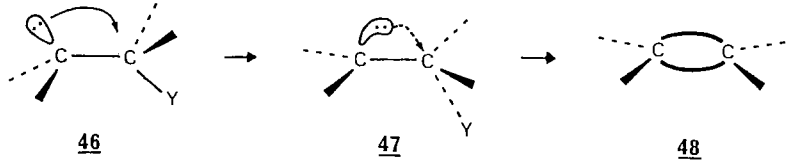
43

44 45

It is pertinent to point out that in internal epoxide opening, six-membered ring formation (21), requires no bending of C – C bonds, while five- (22), four- (28 and 43) and three-membered ring (42) formation requires the simultaneous bending of four, three, and two C – C bonds, in addition to the carbanion electron pair. The degree of bending is of course more pronounced in the formation of the three-membered ring than in the others; consequently, the number of C – C bonds which must bend simultaneously would be more important than the degree of bond bending. In other words, this suggests the simultaneous bending of three C – C bonds (cyclobutane formation) would be less difficult than that of four C – C bonds (cyclopentane formation), but more difficult than that of two C – C bonds (cyclopropane formation).

In that respect, it is interesting to regard a double-bond as a "two-membered" ring, i.e. made of two bent bonds as proposed by Pauling in 1931 (17, see also 18). Its formation requires extensive bending of only one C – C bond in addition to the carbanion electron pair (46 → 47 → 48). So, the ready

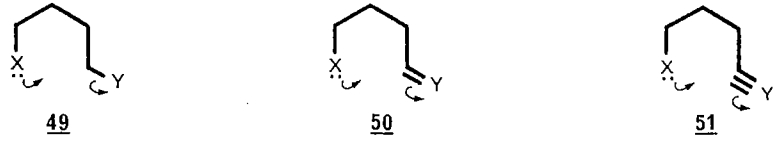
formation of double-bonds could thus be explained. Note also that the anomeric effect (Chapter 1) is the equivalent of what is illustrated by 46 → 47.



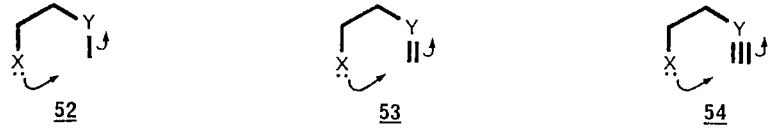
46 47 48

Baldwin (19) has proposed a set of pertinent rules for ring closure. Ring forming reactions are designated by a numerical prefix which denotes the ring size, which is then followed by either the term exo or endo depending on whether the breaking bond is exocyclic or endocyclic (3) to the smallest so-formed ring, and finally by one of the suffixes tet, trig or dig describing the hybridization of the carbon atom undergoing attack in the closure reaction (tetrahedral, trigonal, and digonal, respectively).

For example, the 5-Exo-Tet, 5-Exo-Trig, and 5-Exo-Dig processes are represented by 49, 50, and 51 while the 5-Endo-Tet, 5-Endo-Trig, and 5-Endo-Dig corresponds to 52, 53, and 54 respectively. In this Chapter, we will consider the tetrahedral systems only. The trigonal systems are considered in Chapter 6.

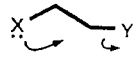


49 50 51



52 53 54

In tetrahedral systems, the possibilities are the following: 3-Exo-Tet to 7-Exo-Tet (55-59) are all favored processes whereas 5-Endo-Tet (60) and 6-Endo-Tet (61) are disfavored on stereoelectronic grounds.



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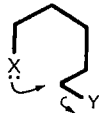
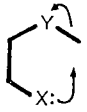


58

59



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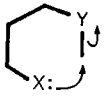
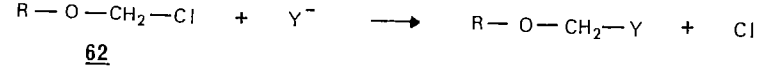


61

The previously described experiment of Eschenmoser (p.164) shows definitely that the 6-Endo-Tet process (61) is indeed not favored. These are numerous experiments in the literature which show that all the Exo-Tet processes are allowed and the relative ease with which these processes take place is the following: 55 > 56 < 57 > 58 > 59. In other words, 55 is easier than 56, and 57 is easier than 56 and 58 while 58 is better than 59. However, Stork has clearly demonstrated that when Y is part of an oxirane ring, this order is changed to 55 > 56 > 57 < 58. Thus, there is a change between 56, 57 and 58, and the fundamental reason is due to stereoelectronic effects.

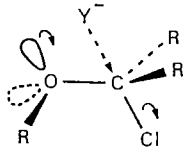
Before completing this section on the SN_2 reaction, we must also consider the influence of the stereoelectronic effects caused by the electron pairs of atoms which are linked to the carbon bearing the leaving group.



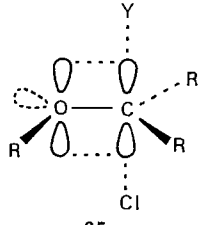
62

63

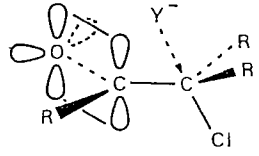
For instance, the rate of SN_2 reaction is greatly enhanced in α-haloethers 62 and in α-haloketones 63. This enhancement should however occur only when the oxygen atom in 62 has an electron pair antiperiplanar to the C—Cl bond (cf. 64 → 65). Similarly, in an α-haloketone the π system of the carbonyl group must be parallel to the C—Cl bond (cf. 66 → 67) (20).



64



65



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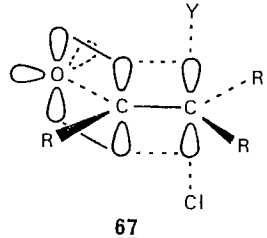
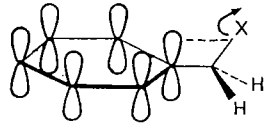


67

It is well known that bimolecular substitution in benzyl substrates (68 → 69) takes place with great ease. This is due to an electronic stabilization of the transition state by conjugation with the aromatic ring (20, 21). The theory predicts that such conjugation will be greatest when the C—X bond of the leaving group is parallel with the p-orbitals of the benzene ring, as in the arrangement 70, and smallest when the C—X bond is orthogonal to the same orbital system as in the arrangement 71.

68 69



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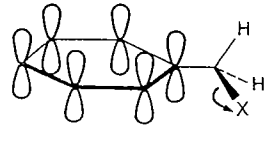
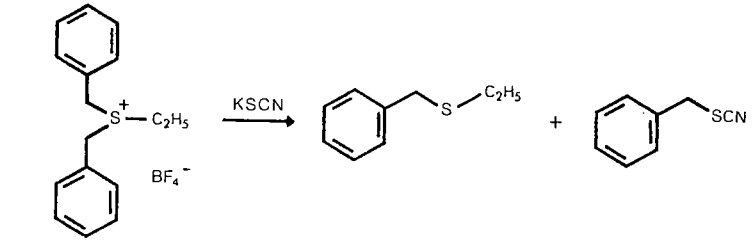
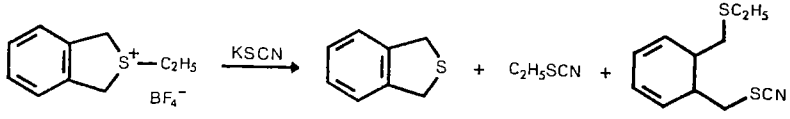


71

King and Tsang (22) have recently studied the relative rate of bimolecular substitution in dibenzylethylsulfonium salt 72 and the cyclic sulfonium fluoroborate salt 75. They found that the reaction of thiocyanate anion with salt 72 which can easily take the arrangement 70 is 8000 times faster than the corresponding reaction with the cyclic sulfonium salt 75, which is tied up in the arrangement 71.



72 73 74



75 76 77 78

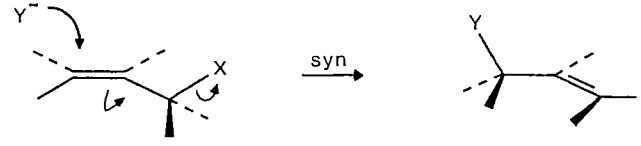
Moreover, product formation was not the same. Dibenzylethylsulfonium salt 72 gave only benzyl ethyl sulfide (73) and benzyl thiocyanate 74, but no dibenzyl sulfide or ethyl thiocyanate. By contrast, the cyclic sulfonium salt 75 gave a mixture containing chiefly (80%) dihydroisothianaphthene (76) with an equivalent amount of ethyl thiocyanate (77) and a minor amount (20%) of the sulfide-thiocyanate 78. This work represents the first direct experimental information on the rate of bimolecular nucleophilic substitution and relative orientation of the benzene ring and the leaving group and it demonstrates clearly the importance of stereoelectronic effects in these reactions.

SN_2' type reaction

Stereoelectronic effects can also be considered in the SN_2' reaction. An excellent review on this topic has been published recently by Magid (23). Although there is still some discussion concerning the concertedness of this reaction, as pointed out by Magid, the stereochemistry of the process

can be analyzed, regardless of the precise timing of the bond-breaking and bond-making steps.

The SN_2' reaction can theoretically take place by a nucleophilic attack on the allylic system either syn or anti to the leaving group (cf. 79 and 80). Although he never fully elaborated on it in print, Winstein (24-26) was the first to postulate that the nucleophilic attack should be syn. He suggested that the approach of the nucleophile displaces the π electrons in such a direction as to allow them to attack the C−X bond from the rear. The syn attack would therefore be favored for stereoelectronic reasons.



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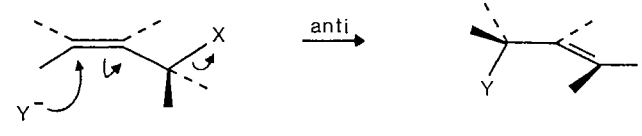


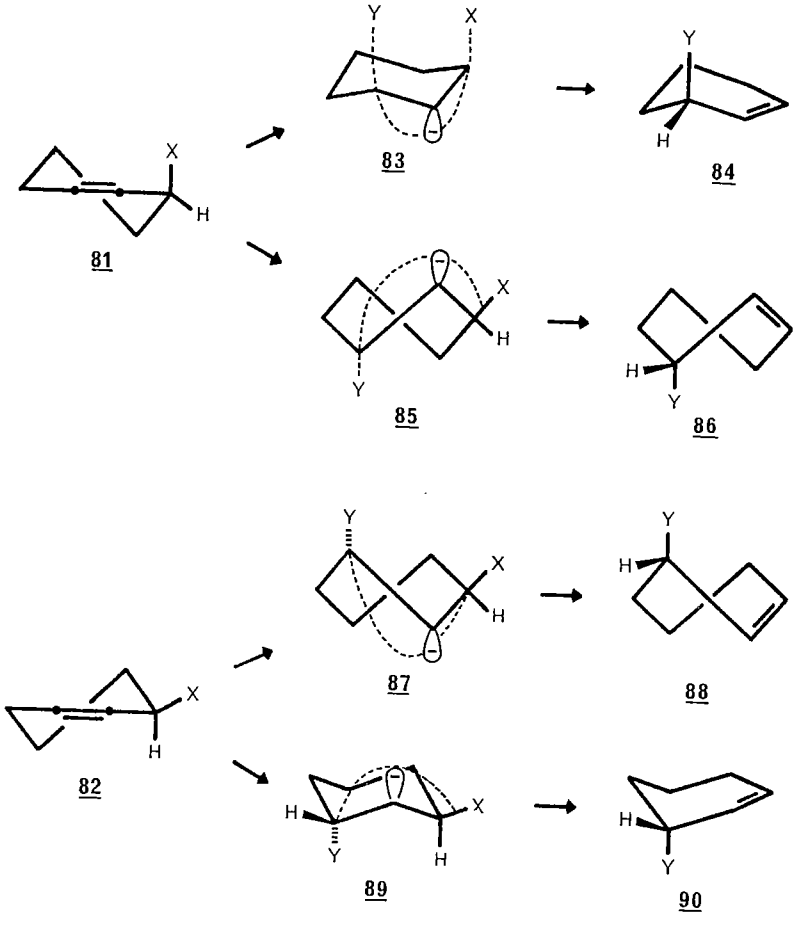
80

A cyclohexenyl system can exist in the two conformations 81 and 82. A syn attack on 81 to give 84 should take place via a transition state having the chair-like stereochemistry 83 where the electron pair is oriented antiperiplanar to the C − X bond. An anti attack on 81 should occur via the twist-boat transition state 85 where the electron pair is syn to the C−X bond, yielding the product in the twist-boat conformation 86. A syn attack on conformer 82 should give 88 via the twist-boat 87 where the electron pair is antiperiplanar to the C − X bond, whereas an anti attack should give 90 via the chair form transition state 89 where the electron pair is syn to the C−X bond.

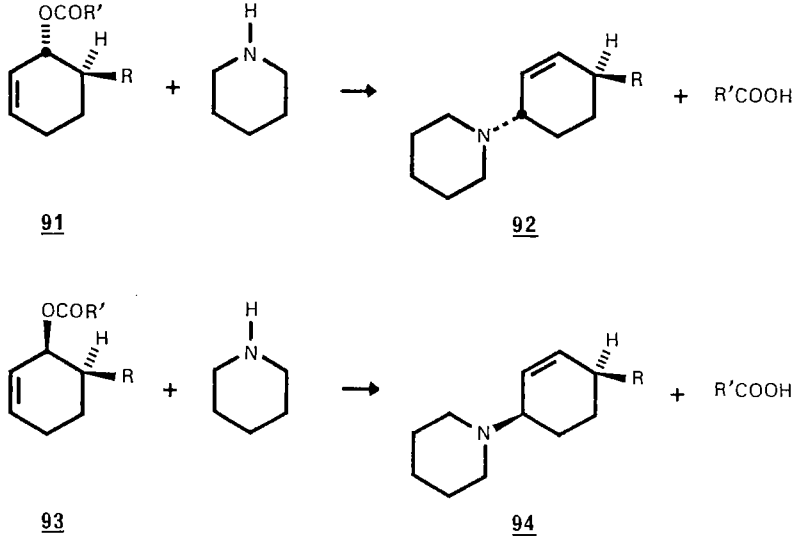
The syn attack on 81 and the anti attack on 82 both lead to the chair-like transition states 83 and 89 so should be favored over the other two processes. Moreover, the transition state 83 which has an electron pair antiperi-

planar to the C – X bond should be favored electronically over transition state 89. Thus, the syn process 81 → 83 → 84 should prevail.

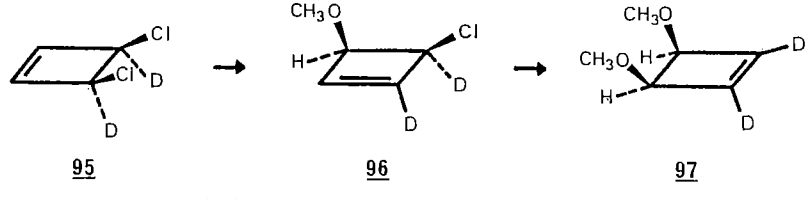
A strong case can be made that all SN_2' reactions should proceed through conformation 81 where the C – X bond is nearly parallel to the p-orbitals of the double-bond. Support for this view comes from the cleavage of protonated cyclohexenols as shown by Goering and co-workers (27, 28). Also, theoretical studies have, for the most part, supported the syn attack notion.



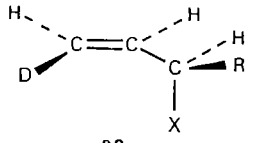
The first experimental study which showed that the SN_2' reaction takes place via a syn mode is due to Stork and White (29). They have observed that the cyclohexenyl dichlorobenzoates 91 (R=CH_3, $CH(CH_3)_2$ or $C(CH_3)_3$ and R'=$Cl_2C_6H_3$–) react with piperidine to give the syn SN_2' product 92. This work was recently confirmed by Stork and Kreft (30) and Dobbie and Overton (31). Also, cis and trans mesitoates 91 and 93 (R'=$C_6H_2(CH_3)_3$, R=$CH(CH_3)_2$) yielded syn SN_2' products 92 and 94 (R=$CH(CH_3)_2$) respectively.



Other experiments confirm the syn SN_2' mode. Kirmse and co-workers (32) have found that cis-dichlorocyclobutene 95 undergoes two consecutive syn SN_2' displacements (→ 96 → 97) with sodium methoxide.



Magid and Fruchey (33) found that the optically active allylic chloride 98 (R=CH_3 and X=Cl) underwent an SN_2' reaction with at least 96% syn stereoselectivity.



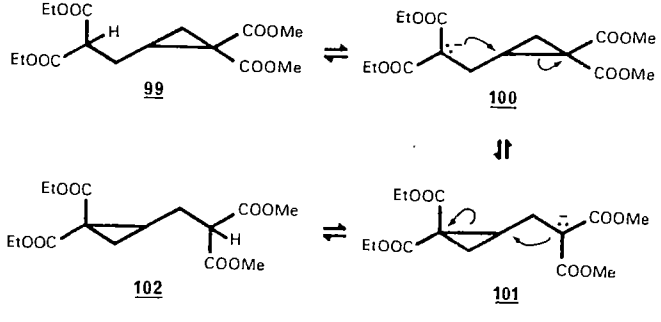
98

However, there are experiments which show that the anti mode can also take place. For instance, changing piperidine for sodium propanethiolate, the trans and cis mesitoates 91 and 93 (R'=$C_6H_2(CH_3)_2$, R=$CH(CH_3)_2$) gave a mixture of syn and anti SN_2' products (30). Also, Oritani and Overton (34) showed that the reaction of dichlorobenzoates 98 (R=CH_3 or C_5H_{11}, and X=$Cl_2C_6H_3CO_2$) with (S)-α-methylbenzylamine gave a mixture of syn and anti SN_2' products (ratio =6:4).

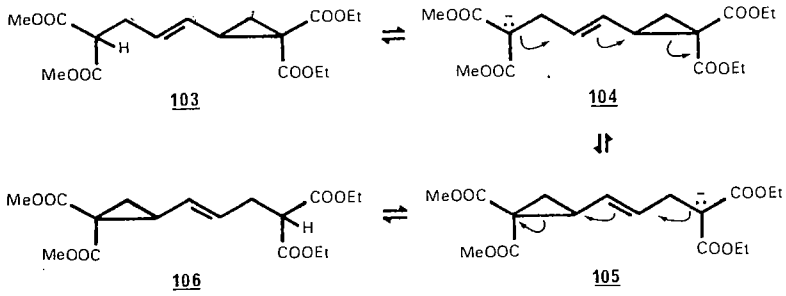
A complete survey of the SN_2' reaction can be found in the review of Magid (23). There are several experiments which clearly show that the syn mode is favored but the anti addition can also take place. The factors which favor the anti mode are not yet completely understood. Nevertheless, there appears to be no doubt that stereoelectronic effects play an important role in these reactions.

Cyclopropane opening

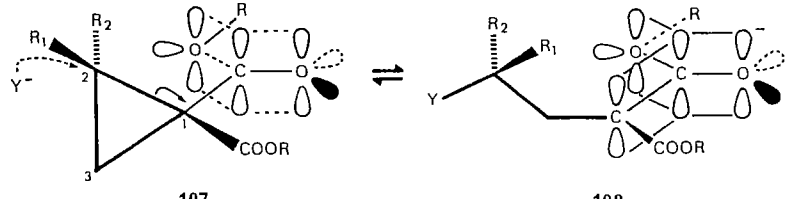
Nucleophilic opening of cyclopropanes doubly activated by alkoxycarbonyl groups is known to take place (see ref. 35 for a review). For instance, in an interesting study, Danishefsky, Dynak, and Yamamoto (36) showed the rapid base catalyzed ($NaCH_2SOCH_3$ in DMSO) interconversion of the two cyclopropanes 99 and 102 via their anions 100 and 101. Danishefsky, Tsai, and



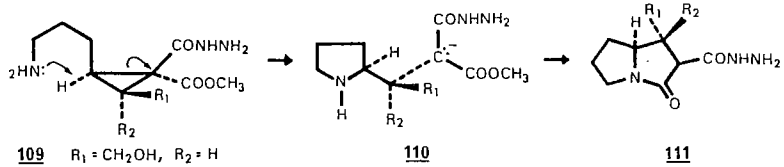
Dynak (37) have further reported the interconversion of 103 and 106 via their respective anions 104 and 105.



These reactions are essentially SN_2 type and take place because the cyclopropane C_2-C_1 bond is parallel to the π system of one alkoxycarbonyl group (cf. 107). As a consequence, the nucleophile attacks the polarized C_2-C_1 bond and inversion at C-2 occurs to give the enolate ion 108. Thus, in the reverse process, i.e. cyclopropane formation, the stereochemistry of the transition state should correspond to 108 → 107. These reactions are therefore controlled by powerful stereoelectronic effects.

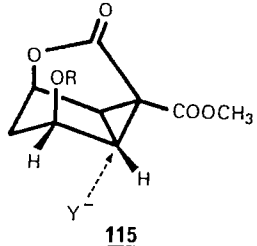


For instance, 109 produced in situ gave 111 via 110 while 112 gave 114 via 113 (38).



109 $R_1=CH_2OH$, $R_2=H$
112 $R_1=H$, $R_2=CH_2OH$

Corey and Fuchs (39) noted the vinyl cuprate addition on 115 to produce 116 stereospecifically. Clark and Heathcock (40) observed the lithium dimethylcopper addition on 117 which yielded 118 while Trost, Taber, and Alper (41) reported the conversion of 119 into 120 with the same reagent.



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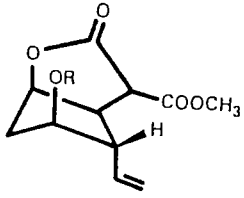

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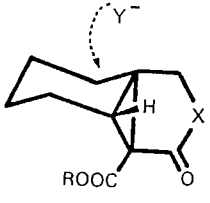
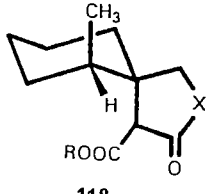


117 X = CH_2 or O



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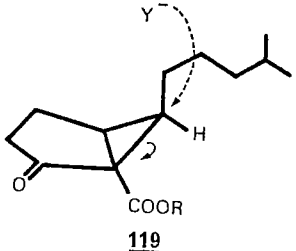

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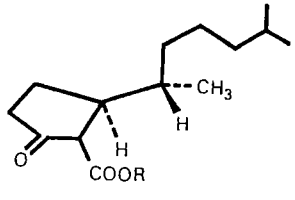
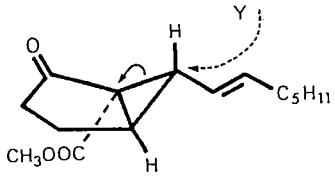


120

Taber (42) and Kondo and co-workers (43) have found the stereospecific opening of 121 → 122 with thiophenoxide. Using phenyl selenide anion as the reagent, Isobe and collaborators (44) discovered the conversion 123 → 124.



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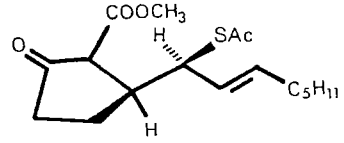

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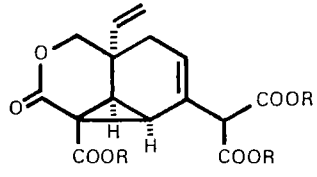
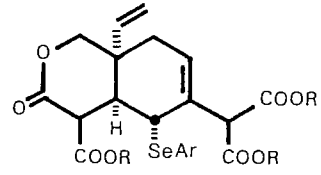
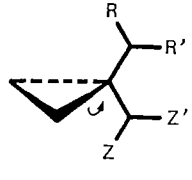


123

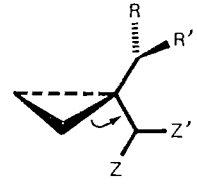


124

In the preceding examples, if both alkoxycarbonyl groups participate in the delocalization of the emerging carbanion, they must take either conformations exo-exo 125A, exo-endo 125B or endo-endo 125C. These conformations are disfavored on dipolar and steric grounds and it is assumed that these compounds react through conformations of type 126 where only one alkoxycarbonyl group (Z'—C—Z) is disposed to facilitate the reaction. Danishefsky and Singh (45) reasoned that if a compound could be designed to exist in one of the conformations of type 125, its reactivity towards nucleophiles should be enhanced. They have verified their conclusion by studying the reactivity of cyclopropane acylals which exist in conformation 125A.

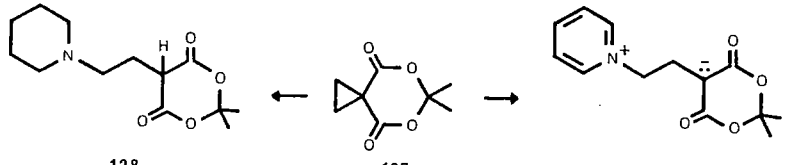


125A R = Z = O; R' = Z' = OR
125B R = Z' = O; R' = Z = OR
125C R = Z = OR; R' = Z' = O

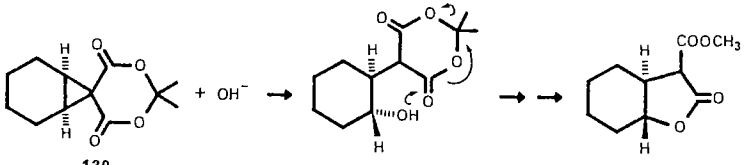


126

They found that 127 reacted exothermically with piperidine in benzene at room temperature yielding adduct 128. Other nucleophilic additions went smoothly (C_6H_5SH, $C_6H_5NH_2$ and $NaCH(COOCH_3)_2$), even the weakly nucleophile pyridine reacted to give the yellow betaine 129. They have also proven that the nucleophilic attack takes place with inversion of configuration. Heating 130 with acetone-water at reflux gave after esterification the trans lactone 131 (46). This series of experiments represents a rather clear demonstration of the importance of stereoelectronic effects in relatior to the reactivity of organic molecules.



128 127 129

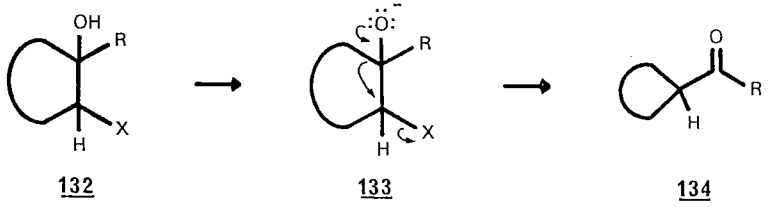


130 131

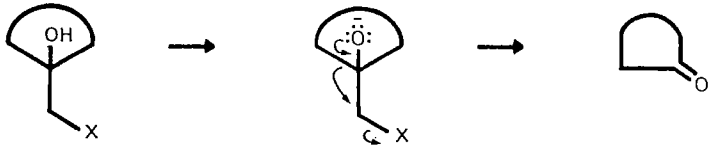
Molecular rearrangements

Cyclic systems with a tertiary hydroxyl group adjacent to a leaving group can undergo a molecular rearrangement in the presence of base yielding either a ring contraction (132 → 133 → 134) (47) or a ring expansion (135 → 136 → 137) (48) product.

In these rearrangements, there are two consecutive internal SN_2 type displacement processes: a) an electron pair of the oxygen atom displaces the electron pair of a C−C bond and b) the electron pair of a C−C bond displaces the leaving group. It is therefore pertinent to find out if these processes follow the stereoelectronic principle of the SN_2 reaction.

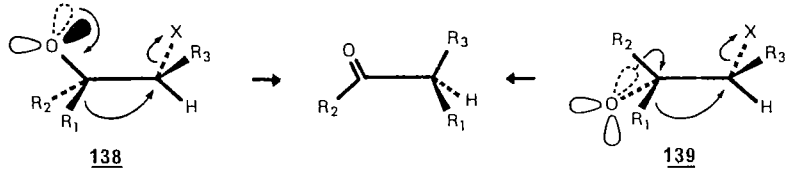


132 133 134

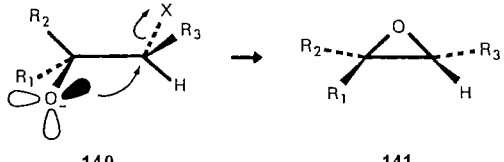


135 136 137

Numerous examples show that the migrating group is always oriented antiperiplanar to the leaving group. For instance, it is the R_1 group which migrates when a compound has a conformation equivalent to that of 138 or 139. Note also that in 138 and 139, the oxygen anion has an electron pair oriented antiperiplanar to the migrating R group. It is also pertinent to point out that when a molecule exists in the third alternative conformation 140, no rearrangement occurs, but the epoxidation process (141) takes place readily. Thus, stereoelectronic effects play a dominant role in these reactions.

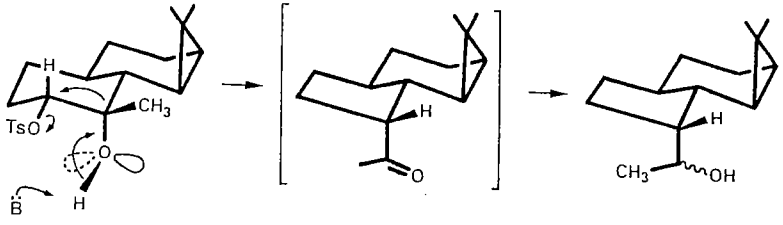


138 139



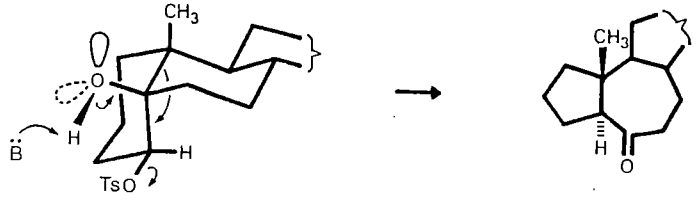
140 141

Only a few examples will be reported here (for a more complete survey, see refs. 47-53). Büchi and co-workers (54) have shown that lithium aluminium hydride reduction of the tosylate 142 gave specifically the ring contracted product 144 via the methyl ketone 143.

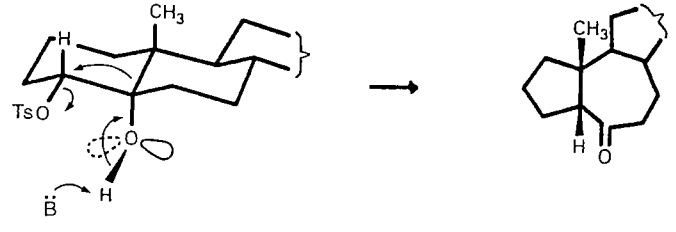


142 143 144

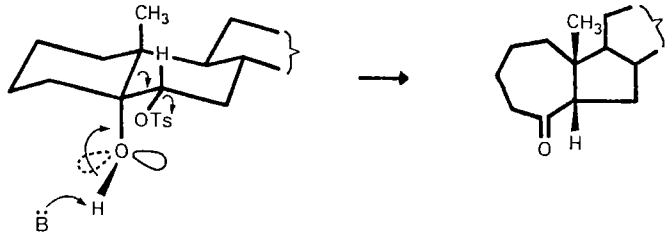
Nussim and Mazur (55) have observed that under mild basic conditions, the steroid derivatives 145, 147, and 149 yield specifically the rearranged ketones 146, 148, and 150 respectively, and Paukstelis and Macharia (56) found that treatment of 151 with sodium methoxide gave nopinone 152. Compounds 142, 145, 147, and 149 correspond to conformation 138 whereas that of 151 is similar to 139.



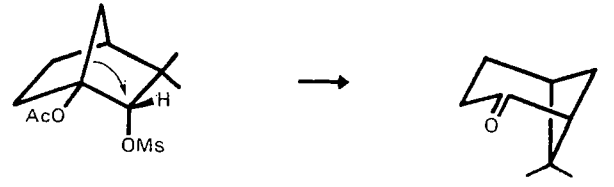
145 146



147 148

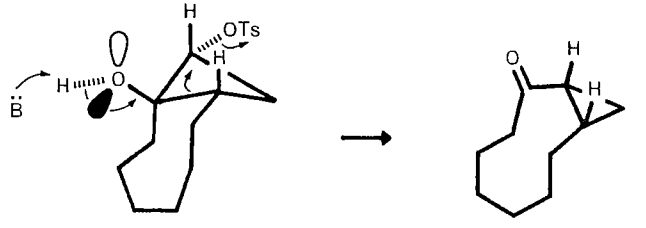


149 150

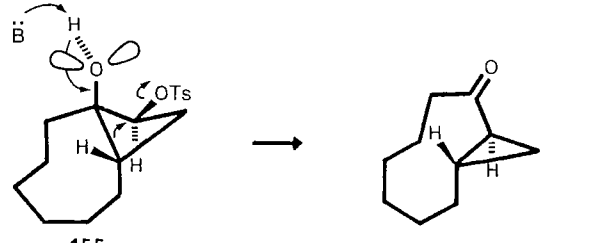


151 152

Also, on passage through alumina, the stereocontrolled ring contraction of tosyloxocyclobutanols 153 and 155 occurs in high yield to give 154 and 156 respectively (57).

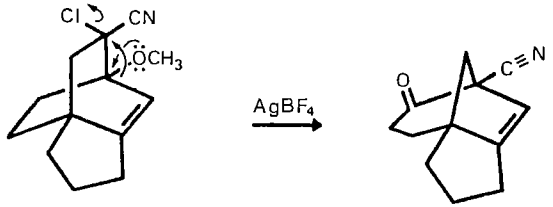


153 154

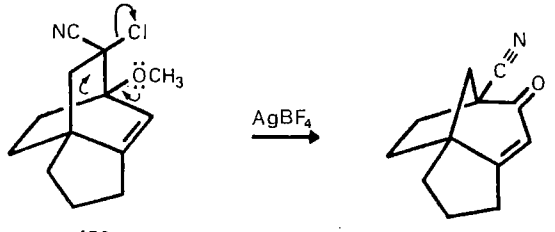


155 156

Interestingly, Yamada and co-workers (58) have shown that the silver ion-promoted rearrangement of the chloronitrile isomers 157 and 159 yields the tricyclic isomeric cyanoketones 158 and 160 respectively.

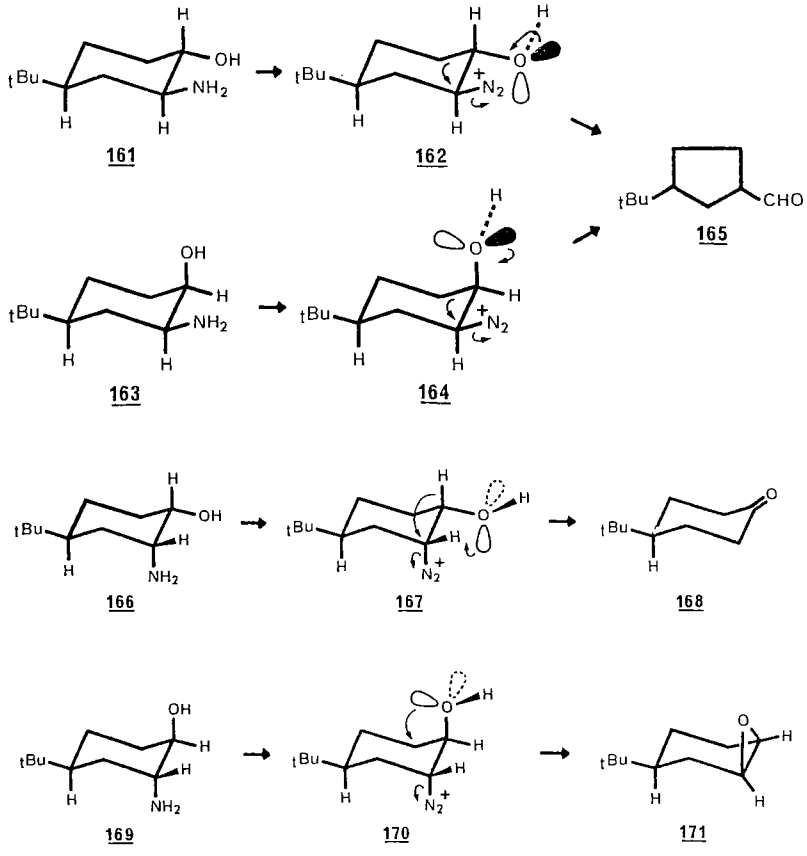


157 158



159 160

The products obtained from the deamination of vicinal aminoalcohols are determined by the conformation of the ground state, where the migrating bond is always oriented antiperiplanar to the C—N bond (59). Indeed, diazotization with nitrous acid of 161 and 163 gave only the cyclopentane aldehyde 165 via the diazohydroxide intermediates 162 and 164 respectively. Diazotization of compound 166 gave the cyclohexanone 168 (98%) via intermediate 167 which undergoes a stereocontrolled internal hydride migration. Finally, the fourth isomer, i.e. 169, gave the cis epoxide 171 via intermediate 170. Favre and Gravel (60, 61) had previously observed that when the amino group can take more than one conformation as in 1-aminomethylcyclohexanols, product formation from the diazotization reaction is directly related to the conformation of the methyldiazonium group.



161 162 165

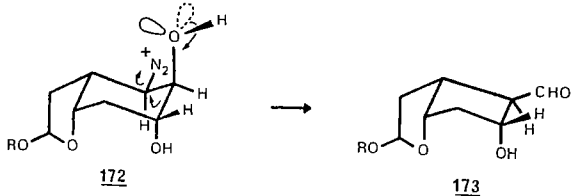
163 164

166 167 168

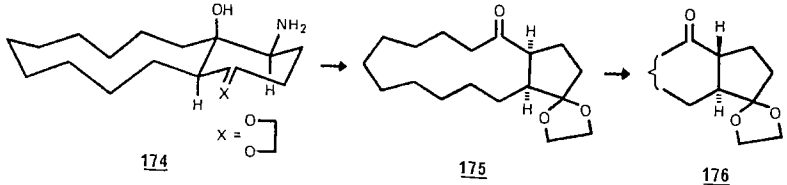
169 170 171

In the Woodward synthesis of prostaglandin (62), intermediate 172 formed in situ from the corresponding amine was smoothly transformed into bicyclic aldehyde 173. Seebach and co-workers (63) have also observed several stereospecific rearrangements using the same reaction. For example, diazotization of amine 174 gave specifically the cis-cyclopentane 175 which was then epimerized into the more stable trans-cyclopentane 176.

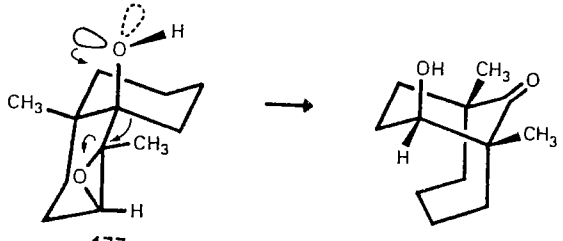
An epoxide oxygen can serve as the leaving group in these rearrangements. For instance, Marshall and Kerschen (64) have found the BF_3 catalyzed transformation 177 → 178.



172 173

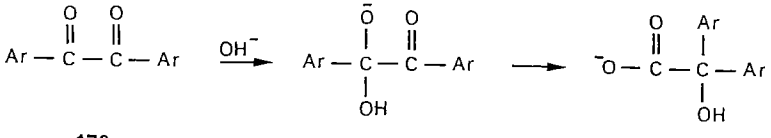


174 175 176

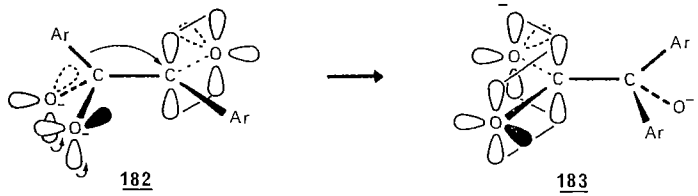


177 178

On the basis of these results, the benzyl-benzylic acid rearrangement 179 → 180 → 181 should occur with stereoelectronic control. The stereochemistry of the transposition should be as depicted by 182 → 183.

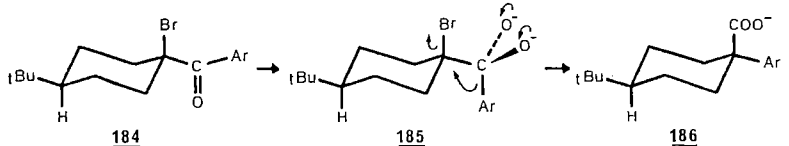


179 180 181

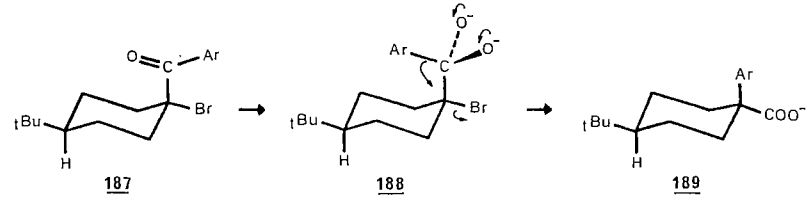


182 183

A similar situation should prevail in the quasi-Favorski rearrangement. Indeed, it has been observed (65) that refluxing compounds 184 and 187 in xylene in the presence of sodium hydroxide gave the isomeric carboxylic acid derivatives 186 and 189 respectively. Thus, there is a neat inversion of configuration of the carbon atom which was initially bearing the halogen atom (cf. 185 and 188).

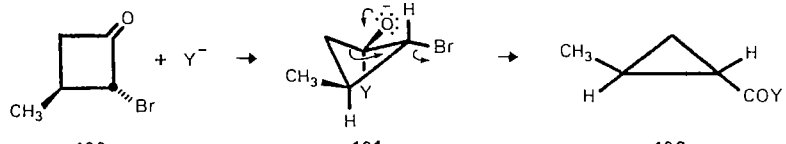


184 185 186



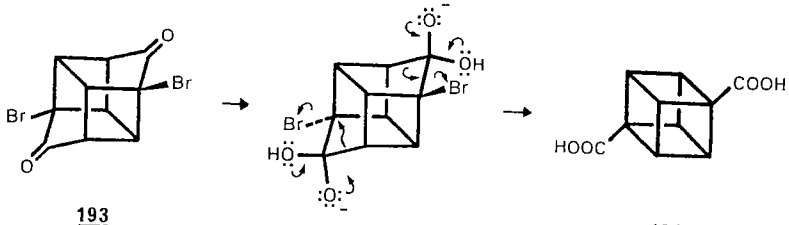
187 188 189

It has also been reported (66, 67) that trans-2-bromo-3-methylcyclobutanone 190 undergoes a stereocontrolled ring contraction to form trans-2-methylcyclopropane derivatives 192 by using either NH_3, aqueous sodium carbonate or water. Inversion of configuration (cf. 191) is again observed.



190 191 192

The double Favorski-like contraction of dibromodiketone 193 (KOH, H_2O; H^+) which yielded p-cubanedicarboxylic acid (194) is another example of this class of ring contraction reaction. This reaction was used by Eaton and Cole (68) in their synthesis of cubane.



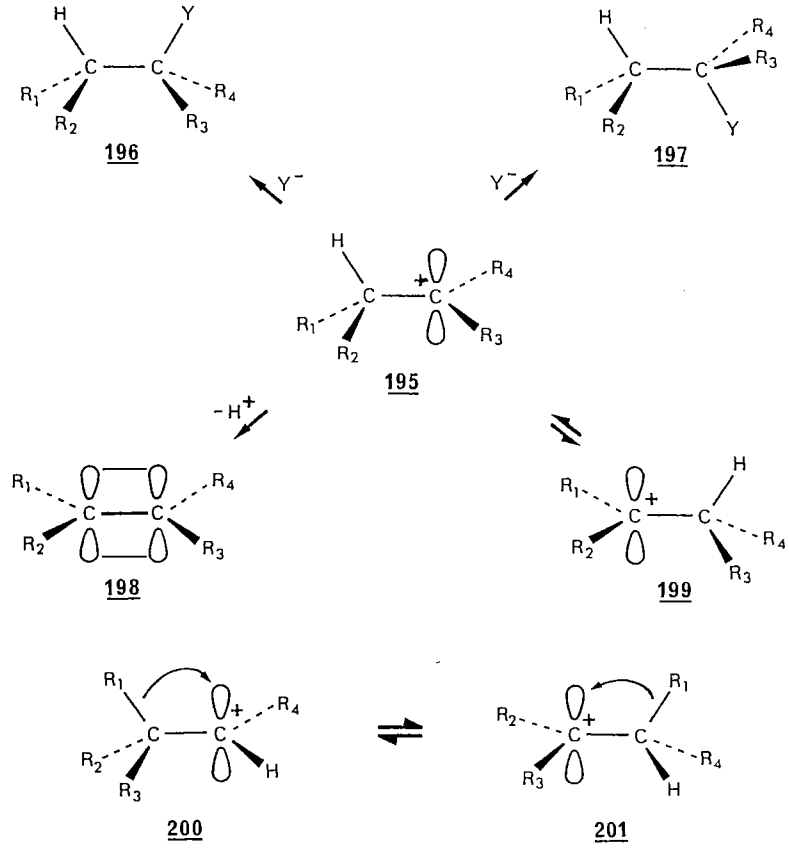
193 194

In these last examples, there are two oxygens each having an electron pair oriented antiperiplanar to the migrating group. This factor should ease the migrating process in a manner similar to that observed in the study of tetrahedral intermediate derived from amides and esters. Note also that the presence of the two negatively charged oxygen atoms in these intermediates is an additional parameter which should facilitate the migration reaction.

Reaction with carbonium ion

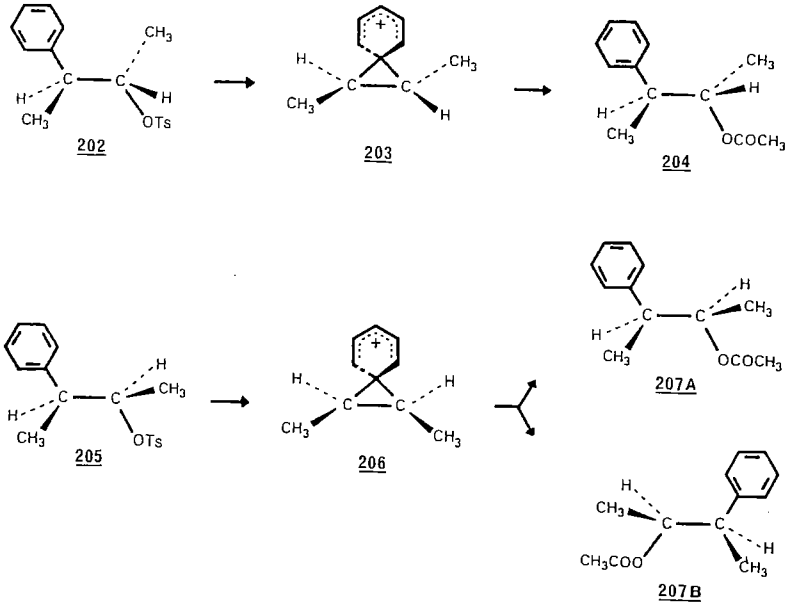
The reactions of carbonium ions occur via transition states having precise stereochemistry in which the electron pair of the attacking nucleophile must be colinear with the empty p-orbital of the electron-poor carbon atom. Thus, powerful stereoelectronic effects control these reactions.

For instance, the attack of a nucleophile Y^- from above or below the plane of a carbonium ion having the conformation 195 will, if $R_3 \neq R_4$, give two diastereomers in conformations 196 and 197 respectively. Carbonium ion 195 can also form a double-bond (→198) by the loss of a proton because the C—H bond is properly aligned with the p-orbital of the carbonium ion. For the same reason, it can also undergo a migration of the hydrogen atom with its electron pair to give the rearranged carbonium ion 199. Similarly, in skeletal rearrangement (47, 48) such as the Wagner-Meerwein or the pinacol transposition, the migrating alkyl group must be that which is properly aligned as shown by 200 and 201.



196 197 195 198 199 200 201

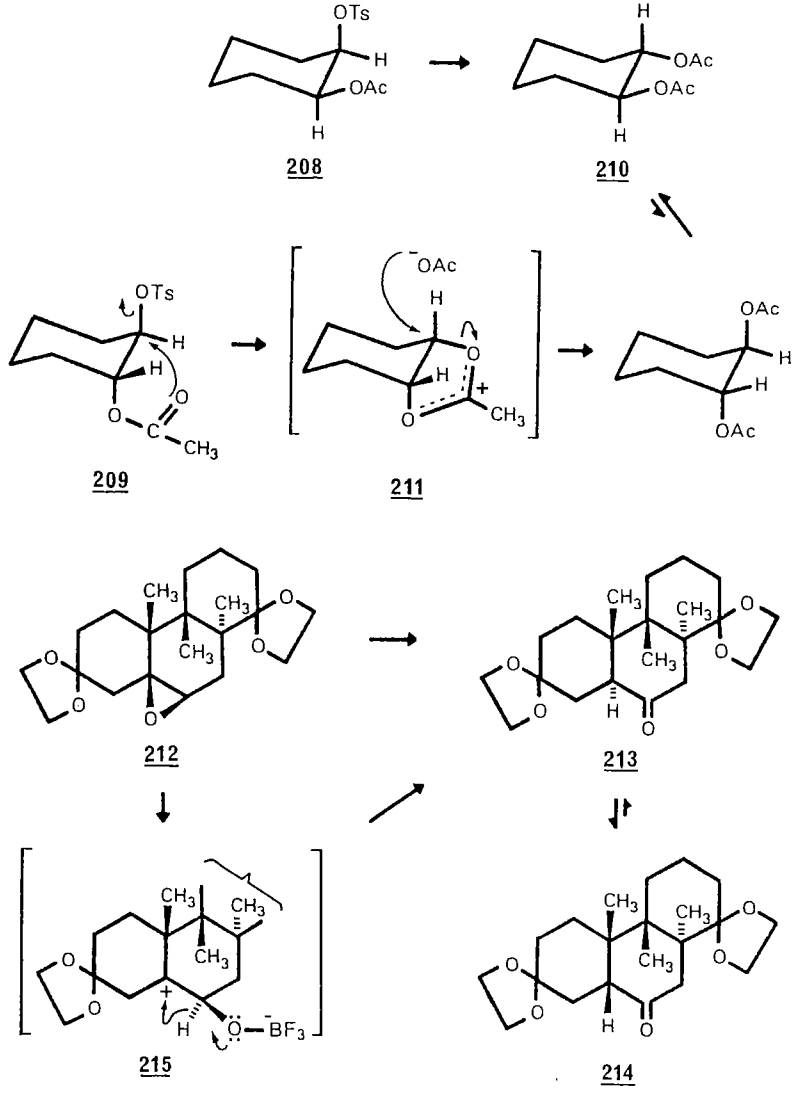
Discrimination can readily be observed between the two possible modes of attack on a carbonium ion (195 → 196 and 195 → 197) when the nucleophile is part of the substrate. In such cases, the phenomenon of neighboring group participation is observed (for a review, see ref. 69). For example, solvolysis of the erythro-tosylate isomer 202 in acetic acid gave largely the erythro-acetate isomer 204 via the chiral bridged ion 203, whereas the threo isomer 205 yielded a racemic mixture of threo products 207A and 207B via the achiral intermediate 206 (70).



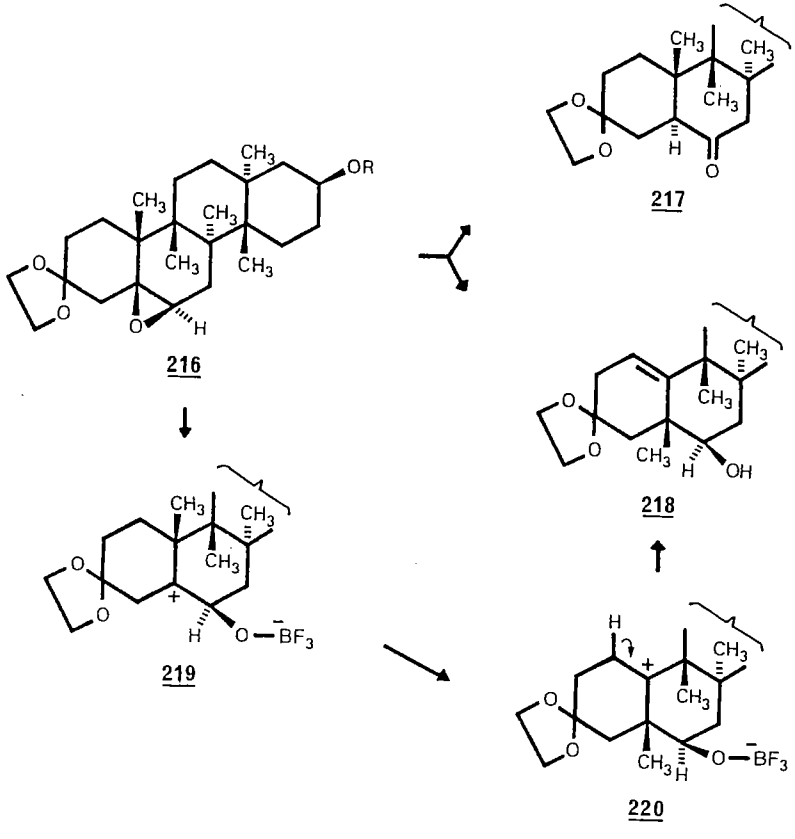
Solvolysis of cis and trans tosylates 208 and 209 gave the same trans diacetate 210 (71-73). The cis isomer 208 undergoes the equivalent of a classic SN_2 displacement of the tosylate by acetate ion to give 210. The trans isomer 209 gives first the cyclic acetoxonium intermediate 211 by the participation of the trans acetate group. Nucleophilic attack of acetate ion on acetoxonium 211 with inversion gives the trans diacetate 210. Interestingly, the rate of solvolysis of the trans isomer 209 is approximately 700 times faster than that of the cis isomer 208 indicating the importance of neighboring-group participation (anchimeric assistance).

Thus, by analyzing the different types of nucleophilic substitution reactions, the stereoelectronic requirements for reactivity and their resulting effects are clearly illustrated. These effects are also seen in simple and complex rearrangement reactions. For example, the following transpositions demonstrate that indeed, the migrating group must be properly aligned as shown by 195 → 199 and 200 → 201. Boron trifluoride catalyzed rearrangement of β-epoxide 212 afforded stereospecifically the trans diketal ketone 213. None of the isomeric more stable cis diketal ketone 214 could be detected. Ireland and Hengartner (74) have interpreted their result as a stereocon-

trolled migration of the α-hydrogen at C_6 in intermediate 215. The stereochemistry of the transition state in 215 → 213 corresponds to that in 195 → 199 (R_2=O $-\bar{B}F_3$).

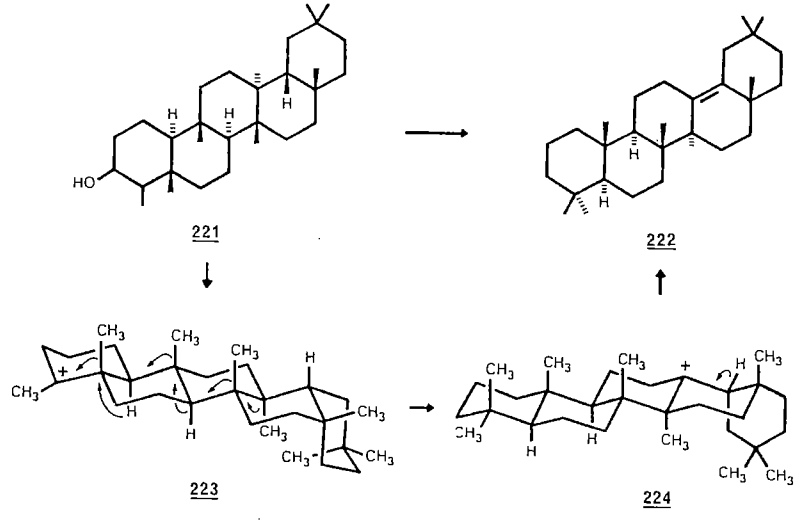


In the case of compound 216, treatment with boron trifluoride etherate gave a mixture of 217 and 218 (75). The transformation 216 → 217 must have occurred via the intermediate 219 as described above. The formation of 218 is the result of the migration of the methyl group followed by the loss of a proton (219 → 220 → 218). These two steps are equivalent to 200 → 201 and 195 → 198.



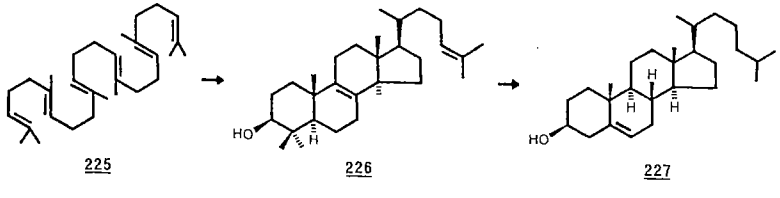
Sometimes, several rearrangements occur consecutively. A spectacular case has been observed (76-79) in the acid-catalyzed transformation of 3-β-friedelanol (221) into 13(18)-oleanene (222). In this case, 221 gave presumably the carbonium ion 223 which underwent six stereoelectronically controlled

1,2 shifts to give the carbonium ion 224 which then looses a proton to yield 222. Also, friedelene, derived from the dehydration of 3-β-friedelanol (221) gave compound 222 on acid treatment.

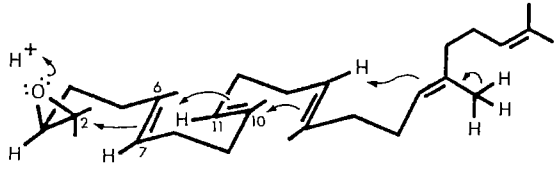


Conclusively, rearrangements of the Wagner-Meerwein type appear to be controlled by powerful stereoelectronic effects.

In the biogenesis of steroids, the enzyme-catalyzed polycyclization of squalene (225) produces the tetracyclic substance lanosterol (226) which is eventually converted into cholesterol (227). Eschenmoser, Stork, and their co-workers (80-82) have proposed that the squalene-lanosterol conversion can be rationalized on the basis of stereoelectronic effects. The stereochemical course of this biological cyclization (83, 84) can be illustrated by considering the transformation of squalene oxide (228) (an intermediate in the biosynthesis of cholesterol (83, 84)) into dammaradienol 229. This transfor-



mation is simpler than the squalene-lanosterol conversion which involves some rearrangements of carbon atoms.



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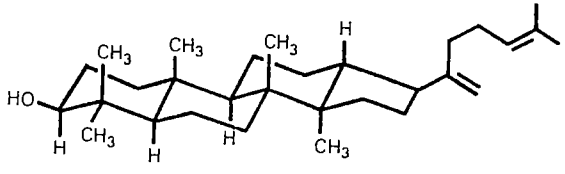


229

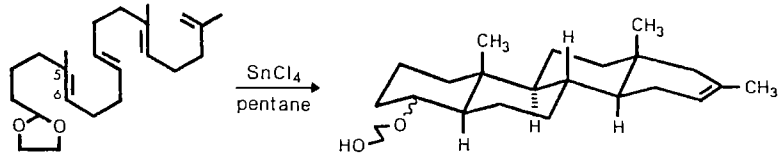
The writer has chosen Johnson's summary to describe the basic ideas (85-87). The process may be regarded as involving trans-antiparallel electrophilic additions to the olefinic bonds in the same stereochemical sense that bromine adds stereospecifically to alkenes. Thus, protonation of the oxygen of the squalene-epoxide 228 generates an incipient cationic center at C-2 which reacts with the π electrons of the 6,7-olefinic bond forming a sigma bond between C_2 and C_7. The cationic center developing at C-6 initiates an electrophilic attack on the 10,11-olefinic bond generating the $C_6 - C_{11}$ sigma bond, etc. Consequently, the all-trans geometry of the olefinic bonds in squalene results in the formation of product 229 having the four rings trans-fused. This general concept of stereoelectronic control of polyene cyclization provides a satisfactory rationalization of the stereochemical course of many biological cyclizations.

In a brilliant series of experiments, Johnson and co-workers have discovered that the treatment of certain polyolefins having trans olefinic bonds in a 1,5-relationship can produce stereospecific, non enzymic, cationic cyclization products with the all-trans configuration. These transformations

appear to mimic in principle the biogenetic conversion of squalene into polycyclic triterpenoids. This work has been well reviewed (85-87) and only a few representative examples will be described here.

This type of carbon-carbon bond formation occurs through the interaction of double bonds with carbonium ions. It can be viewed as a sort of displacement reaction forming sigma C — C bonds, and it is for this reason that it is described in this Chapter.

Treatment of polyolefinic ketal 230 with stannic chloride in pentane gave a mixture (30% yield) of about equal amounts of the two racemic D-homosteroidal tetracyclic isomers 231 (88). In this cyclization, the first cationic intermediate is not chiral and the two faces of the 5,6-double-bond can react with equal facility with the carbonium ion; as a consequence, the product obtained (231) is necessarily racemic. The conversion of the open-chain tetraenic acetal 230 having no chiral centers into a tetracyclic system having seven such centers and producing only two (231) out of a possible 64 racemates is a striking tribute to the power of stereoelectronic effects.

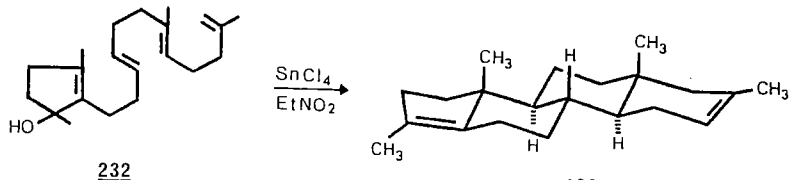


230 231

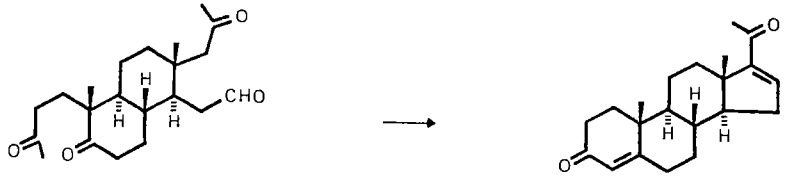
Another example is the cyclization of the racemic allylic alcohol 232 at -80°C which furnished the racemic tetracyclic bis-olefin 233 in 70% yield (89, 90). Ozonolysis of 233 gave the bicyclic triketone aldehyde 234 which underwent under acidic conditions a double intramolecular aldol cyclodehydration to produce racemic 16,17-dehydroprogesterone 235. This represents the first synthesis of a steroid via the now so-called "biomimetic" polyene cyclization method.

Cyclization of the tetraene 236 with trifluoroacetic acid in dichloromethane at temperatures of -50° to -25° gave yields of 237 up to 81% when Ar=α-naphthyl (91). The stereospecific formation of the cis-fused A/B ring junction is a direct consequence of stereoelectronic control. Indeed, in the formation of the cis junction, the newly formed bond (238 + 239) is pseudo-axial and is therefore maintained parallel to the π-orbital of the cyclohexenyl double-bond. Such orbital overlap is impossible in forming an A/B

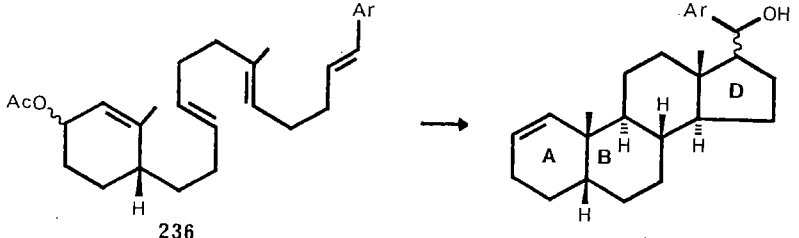
trans ring junction as the new formed bond would be pseudoequatorial. The five-membered ring D is produced because the resonance-stabilized benzyl cation 240 is formed in preference to the six-membered ring homobenzylic cation 241.



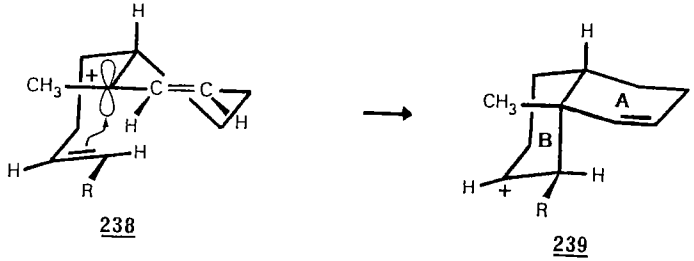
232 233



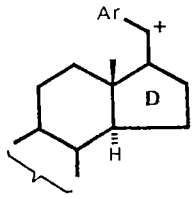
234 235



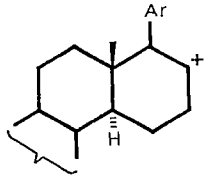
236 237



238 239

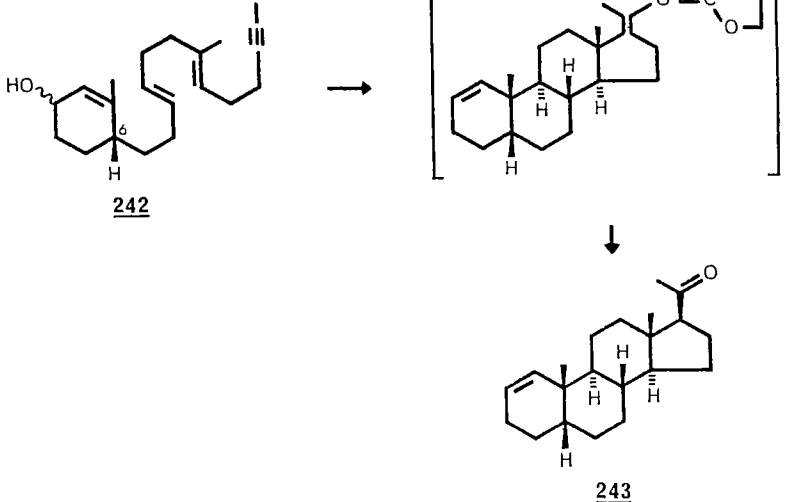


240



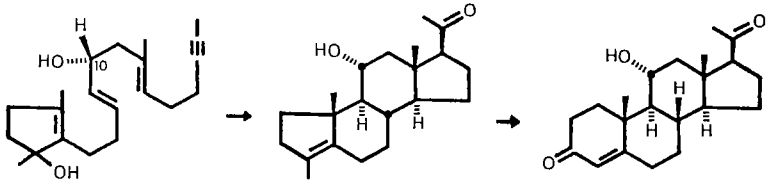
241

Johnson and co-workers (92) have recently reported the cyclization of the D-allylic alcohol 242 (optical purity of 91%). When the substrate 242 was treated with trifluoroacetic acid in 1,1-difluoroethane containing ethylene carbonate, a 65% yield of Δ^1-5β-pregnen-20-one (243) was obtained with an optical purity of 91%. In a similar fashion, the enantiomer of 242 gave the enantiomer of 243 with an optical purity of 92%. Very little racemization has occurred and the cyclization step is essentially enantiospecific. Again, the A/B ring junction is cis and the process involves essentially total asymmetric synthesis due to the C-6 chiral center in 242.



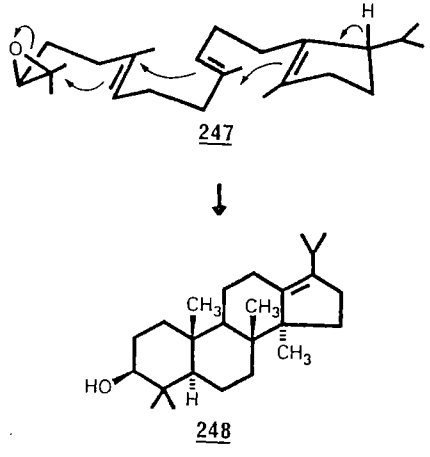
242 243

In another study (93), cyclization of optically active substrate 244 gave optically active tetracyclic product 245 with the same optical purity. Since, 245 was converted into 11α-hydroxyprogesterone (246), this work constitutes a total asymmetric synthesis of that steroid. This remarkable asymmetric control is due to the chiral center at C-10 of 244: the relative orientation of the hydroxyl group in the transition state of the cyclization process, controlled by stereoelectronic factors, is such that it yields a product (245) having an equatorial secondary alcohol.



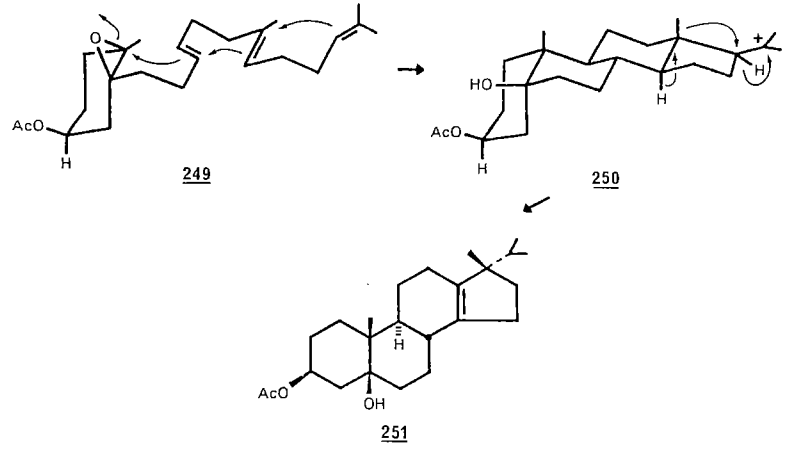
244 245 246

Van Tamelen has examined extensively the cyclization of monoepoxide-polyolefins (94). For example, he found (95) that the treatment of racemic epoxide 247 with $SnCl_4$ in nitromethane provided a major product (35% yield) which was identified as the racemic tetracycle 248. This represents an overall, close simulation of the squalene → tetracyclic triterpene bioconversion (except for optical activity).



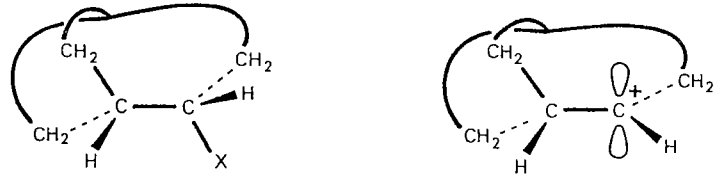
247 248

In another example, van Tamelen and Loughhead (96) have carried out the cyclization ($BF_3 \cdot Et_2O$) of (±)-monocyclic epoxide 249 at low temperature which yielded the tetracyclic alcohol 251 in 25% yield. This can be explained by the formation of cation 250 which is the precise result predicted by the stereoelectronic theory on epoxide opening (producing a cis A/B ring junction) and polyene cyclization (yielding a trans junction for ring B, C, and D). The compound 251 is then formed by the appropriate migrations and proton elimination steps (see arrows in 250).



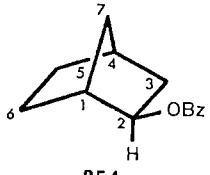
249 250 251

An interesting situation arises when a carbonium ion (generated by solvolysis, i.e. 252 → 253) is next to a bridgehead carbon atom. Very often, one of the C—C bonds of the bridgehead is oriented co-planar with the p-orbital of the cation 253 (or antiperiplanar to the leaving group in the starting product 252). As a consequence, an electronic delocalization of the electron pair of the C — C bond with the cation (or with the developing cation) is possible. This stereoelectronic effect should therefore strongly influence the formation (and the reactivity) of the resulting carbonium ion.

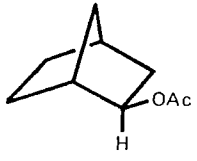


252 253

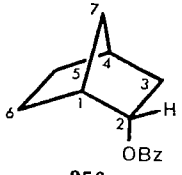
For example, acetolysis of exo-2-norbornyl brosylate 254 produces exclusively exo-2-norbornyl acetate 255. The exo-brosylate 254 is more reactive than the endo-brosylate 256 by a factor of 350 and the acetolysis of optically active exo-brosylate gave completely racemic exo-acetate 255. Thus, the carbonium ion produced from exo-254 is more rapidly (thus more easily) formed than that from endo-256. These results were originally rationalized in term of a bridged (nonclassical) cation 257 (Winstein approach) (97) or as the rapidly equilibrating classical carbonium ions 258 and 259 (Brown approach (98, 99)).



254



255



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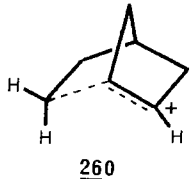
259

It is presently accepted that there is an electronic delocalization and the problem is to describe precisely the nature of that delocalization. In one view, it is described by C−C hyperconjugation involving little geometrical change (cf. 260) (100-103) or more recently by 1,3-bridging (cf. 261) (104-106). The other view (107) is that in some cases, a partially bridged structure exists in which significant but unequal bonding to a second atom is taking place (unsymmetrical bridging, cf. 262) (108, 109) and in others, strong and equal bonding of the bridging atom to two atoms occurs (symmetrical bridging, cf. 263) (110, 111).



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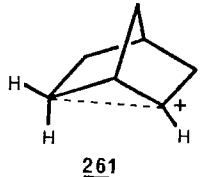
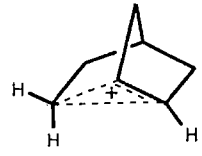
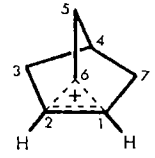


261

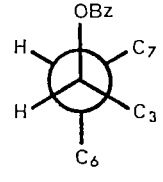


262

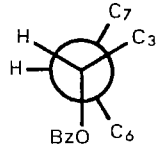


263

It is not the intention here to decide between these views but to indicate that either approach involves strong stereoelectronic requirements. As pointed out recently by Grob and co-workers (112), the extent of electronic delocalization must depend on the alignment of the participating sigma bond with the leaving group. The Newman projections 264 and 265 illustrate the bond alignment in 254 and 256 respectively. In projection 264, the $C_1 - C_6$ bond is perfectly antiperiplanar to the leaving group and it can therefore assist the ejection of that group effectively. In 265, the $C_1 - C_7$ bond is not antiperiplanar and provides less stabilization in the transition state, so the endo isomer 256 is solvolyzed at a slower rate than the exo isomer 254.



264



265

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CHAPTER 6

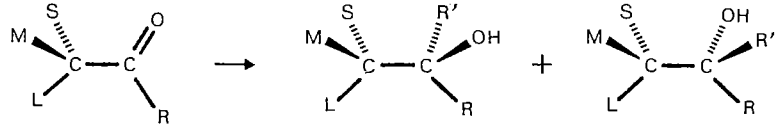
REACTIONS ON SP_2 TYPE UNSATURATED SYSTEMS

NUCLEOPHILIC ADDITION

Ketones and aldehydes

We have already discussed in Chapter 2 that nucleophilic addition to a carbonyl group is controlled by stereoelectronic effects. Both X-ray data and theoretical calculations indicate a clearly defined path (cf. p. 32) for the attack of a nucleophile on a carbonyl group. Baldwin (1) has also used a vector analysis approach to predict the stereochemistry of the addition products.

The reactions of hydrides and Grignard reagents with simple open-chain aldehydes and ketones 1 (L, M, S, and R being groups containing carbon and hydrogen only) are known to lead predominantly to the diastereoisomers 2 as predicted by Cram's rules (2-4). A modification of the interpretation of these experimental results was published by Chêrest, Felkin, and Prudent (5).

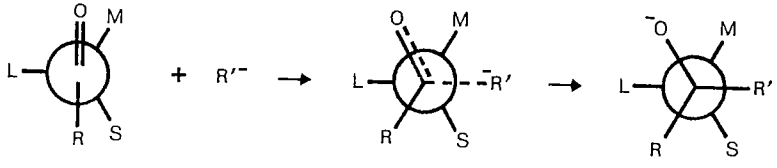


1 2 3

Both interpretations are based on the fact that the nucleophile must attack the carbonyl group perpendicularly (a consequence of stereoelectronic con-

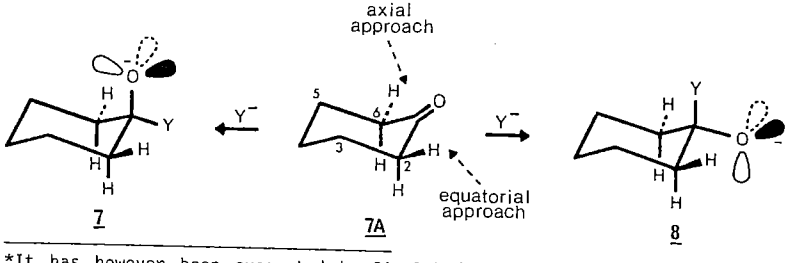
trol), and the preference for the formation of diastereoisomer 2 is due to steric effects.

In the Felkin model (5), the important steric interactions involve R'⁻ and R rather than the carbonyl oxygen as assumed by Cram (2-4) and also Karabatsos (6). On this basis, the preferred mode of attack is 4 → 5 yielding 6, the least strained of six possible staggered conformations (three staggered conformations are possible for each of the diastereoisomers 2 and 3; 6 is equivalent to the least strained conformation of 2). Recently, Anh and Eisenstein (7) have concluded from their ab initio calculations that the transition 4 → 5 → 6 does indeed correspond to the minimum energy transition state.



4 5 6

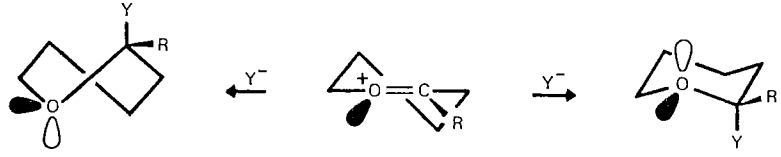
When the carbonyl group is exo to a ring as in cyclohexanone, both the equatorial and the axial approach can lead to a chair intermediate (cf. 7 and 8) with stereoelectronic control because, in each case, the oxygen atom has an electron pair antiperiplanar to the C−Y bond. So, in this case, one process is favored over the other solely on the basis of steric effects and torsional strain due to the presence of the ring (8).*



7 7A 8

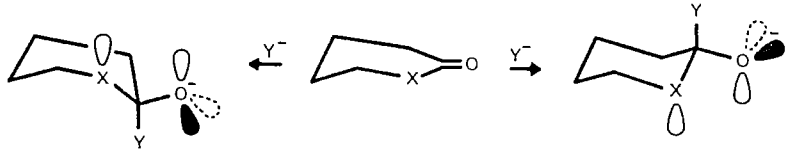
*It has however been suggested by Cieplak (9) that the stereochemistry of nucleophilic addition to cyclohexanone is determined by a combination of steric and stereoelectronic effects. According to this interesting model, steric hindrance favors the equatorial approach while electron donation favors the axial approach. The stereoelectronic effect favors the axial approach because the axial C−H bonds next to the carbonyl group (C_2-H_a and C_6-H_a) are better electron donors than the C_2-C_3 and C_5-C_6 α bonds (cf. 7A → 7 and 7A → 8).

The situation is however different when the carbonyl group is part of a ring as in oxonium ion 9. The attack from the bottom face of 9 leads to a chair intermediate 10 while that from the top face leads to a twist-boat 11. The attack from the bottom face of 9 is therefore strongly preferred for stereoelectronic and steric reasons.



11 9 10

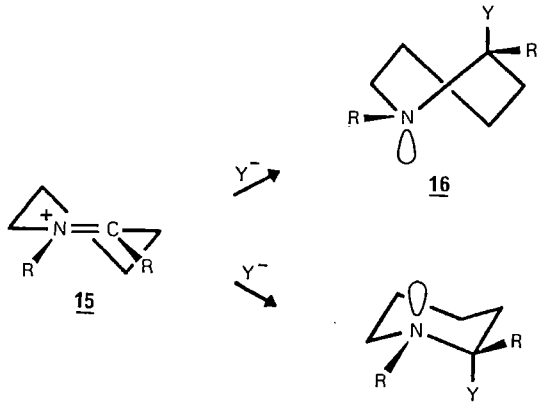
The oxygen atom in 9 can be replaced by sulfur, and the same prediction is maintained. We have already seen that this is indeed the case for cyclic oxonium and sulfonium ions (Chapter 2). It is essentially for the same reason that lactones, thionolactones (Chapter 3) as well as lactams and their derivatives (Chapter 4) behave in exactly the same manner. Indeed, an axial attack on 12 (X=O, S, or NR) leads to an intermediate having a chair conformation (12 → 13) while an equatorial attack necessarily leads to the less favorable boat conformation (12 → 14).



14 12 13

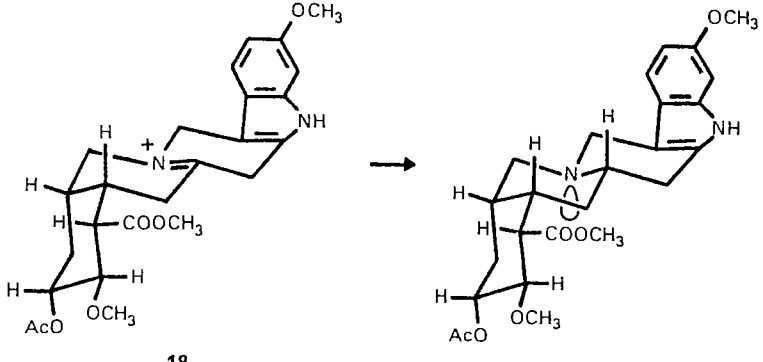
Iminium salts

The reaction of nucleophiles with the conformationally rigid piperidinium ion 15, like that with cyclic oxonium ions, can also be controlled by stereoelectronic effects. On that basis, the addition of a nucleophile on the upper face of 15 must lead to the boat-like intermediate 16 whereas that from the lower face must lead to the chair-like intermediate 17. The transition state leading to 16 must be less favorable than that leading to 17 and product 17 should therefore be favored.



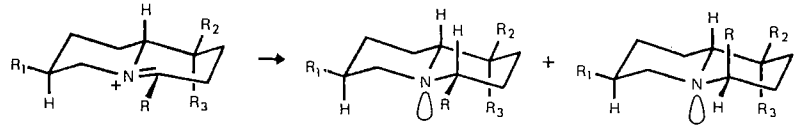
15 16 17

In the total synthesis of reserpine, Woodward and collaborators (10) have reported that the quaternary iminium salt 18 was reduced with aqueous methanolic sodium borohydride to methyl O-acetyl isoreserpate (19). This is the anticipated product whether the stereochemical sense of the reaction is subject to steric or thermodynamic control as pointed out by Woodward. It is also the expected one on the basis of stereoelectronic control.



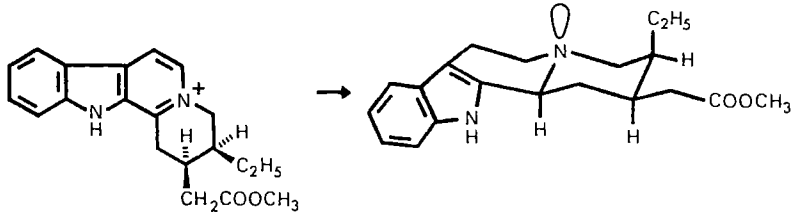
18 19

Bohlmann and co-workers (11, 12) have shown that the borohydride reduction of iminium salts of type 20 gave product 21 in preference to its isomer 22. These results indicate that there is stereoelectronic control in these reductions as discussed by Toromanoff (13).

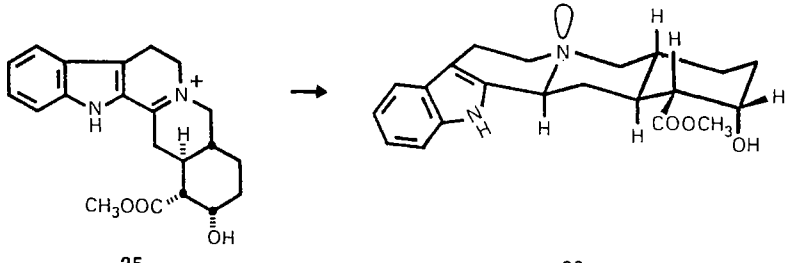


20 21 22

This is confirmed by Wenkert and collaborators (14) who showed that the borohydride reduction of compound 23 gave 24. Similarly, Stork and Guthikonda (15) observed that the reduction of 25 (produced in situ) gave (±)-yohimbine (26).

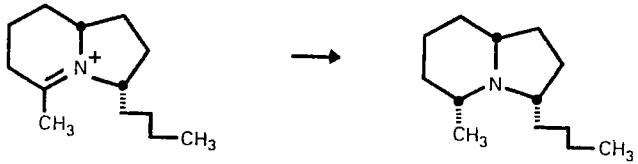


23 24



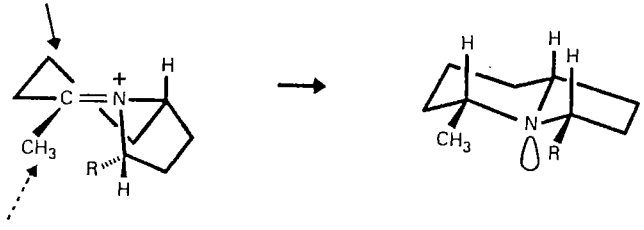
25 26

Stevens and Lee (16) have recently completed a stereospecific synthesis of (±)-monomorine (28). In the last step of this synthesis, the piperidinium ion 27 was reduced with sodium cyanoborohydride to give only (±)-monomorine (28).

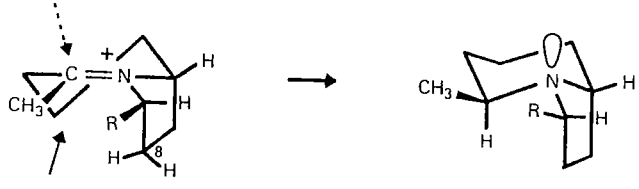


27 28

There are four possible transition states in the reduction of 27 wherein maximum orbital overlap can be maintained with respect to the attacking hydride reagent and the developing electron pair on nitrogen. Two of these (cf. dotted arrow in 29 and 30) require boat-like transition states in order to satisfy the stereoelectronic requirements and are unfavorable kinetically. Of the two possible chair-like transition states (cf. solid arrow in 29 and 30) the latter suffers from a strong steric interaction between the nucleophile and the C-8 pseudo-axial hydrogen. The process 30 → 32 is thus disfavored by comparison with the process 29 → 31.



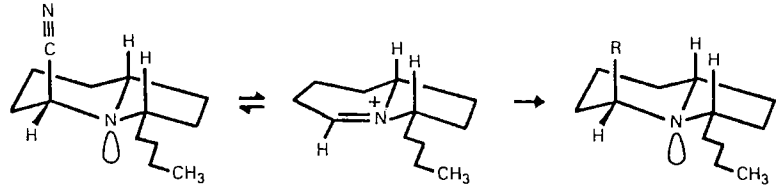
29 31



30 32

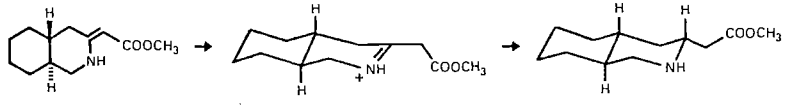
In another interesting study which led to a stereospecific synthesis of one of the stereoisomer of gephyrotoxin-223, Stevens and Lee (17) found that the reaction of piperidinium ion 33 with cyanide led to axial cyanoamine 34 in 96% yield. The cyanoamine 34 also served as a latent form of salt 33.

The reaction of 34 with excess Grignard reagent (CH_3MgBr or $CH_3CH_2CH_2MgBr$) led stereospecifically to the axially oriented isomer 35 (R=CH_3 or $CH_3CH_2CH_2$) in high yield. The high degree of stereoselectivity observed is again in complete agreement with the preceding argument (29 → 31) based on the principle of stereoelectronic control.



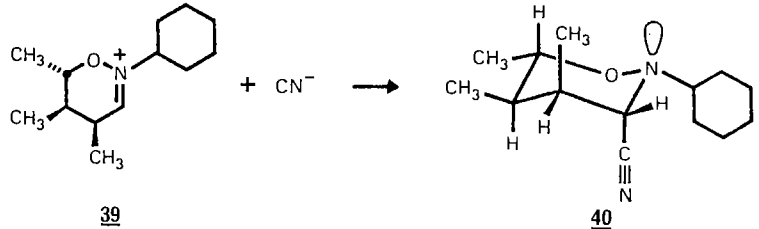
34 33 35

Reduction of vinylogous carbamate 36 with sodium cyanoborohydride in acidic methanol gave exclusively the equatorial aminoester 38. Eschenmoser and co-workers (18) have explained this result by invoking a stereoelectronically controlled antiperiplanar addition of hydride ion on the iminium ion 37.

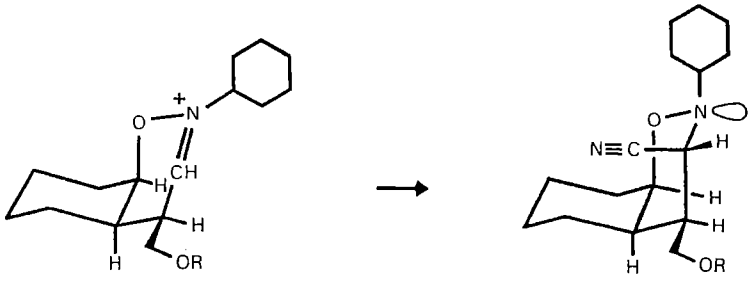


36 37 38

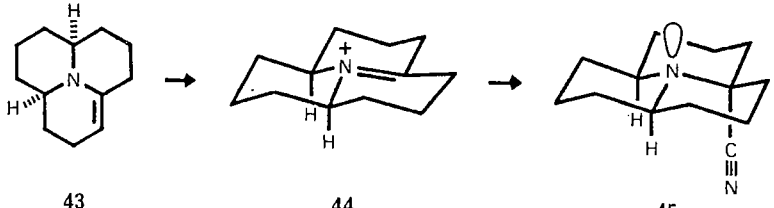
Petrzilka, Felix, and Eschenmoser (19) have shown that the reaction of cyanide ion on the ion 39 gave mainly the addition product 40. Similarly, Riediker and Graf (20) observed that the addition of cyanide on the ion 41 gave preferentially 42 which is the result of a stereoelectronically controlled reaction of the most hindered face of the iminium ion. Stereospecific addition of cyanide to enamine 43 via the iminium salt 44 to yield compound 45 has also been reported (21).



39 40

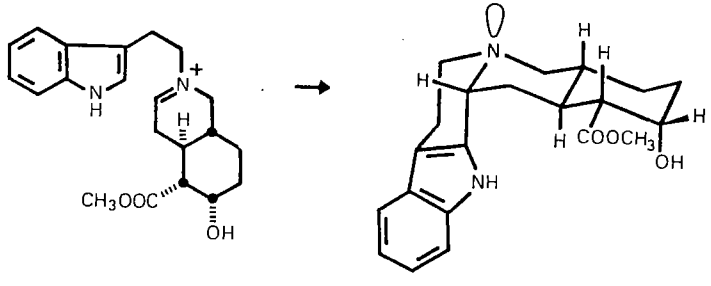


41 42

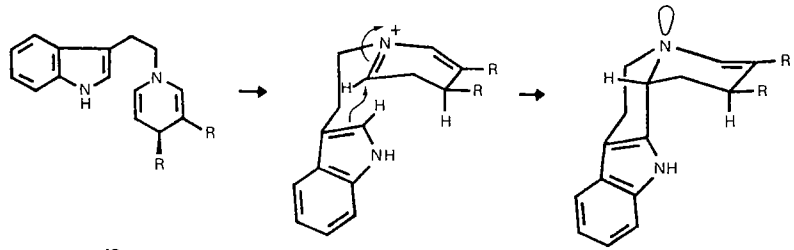


43 44 45

Stork and Guthikonda (15) have shown that the cyclization of iminium ion 46 (produced in situ) gave (±)-ß-yohimbine (47) and Wenkert and co-workers (22) have further observed that the acid-catalyzed cyclization of enamines of type 48 yielded exclusively product 50 via the cyclization of iminium ion 49. In the last two examples, formation of the C—C bond is the result of a trans-addition on the iminium double-bond in agreement with the principle of stereoelectronic control.

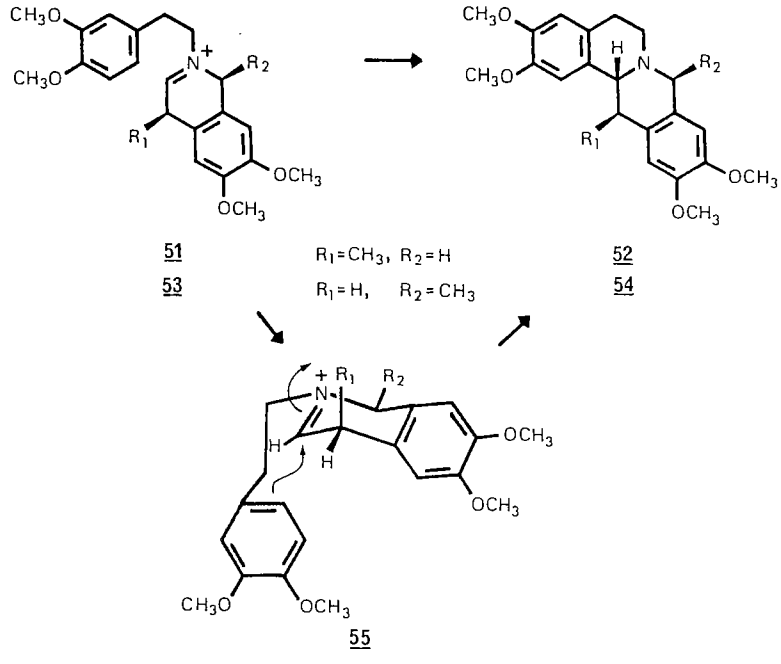


46 47



48 49 50

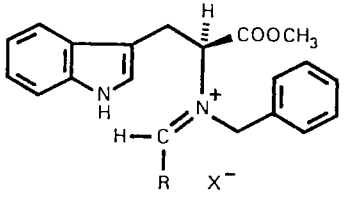
Dean and Rapoport (23) have reported the stereospecific cyclization of iminium ion 51 to give the cis isomer 52. Similarly, cyclization of iminium ion 53 gave 54 exclusively. Cyclization must therefore occur as shown by 55.



51 $R_1=CH_3$, $R_2=H$ 52
53 $R_1=H$, $R_2=CH_3$ 54

55

Cook and collaborators (24) have shown that the Pictet-Spengler condensation of iminium salts of structure 56 (R=alkyl or aryl group) gave only the trans isomer 57 and in high yield. This result can be explained if the stereochemistry of the transition state corresponds to 58 → 59 where the principle of stereoelectronic control is respected and where the steric effects are reduced to the minimum.



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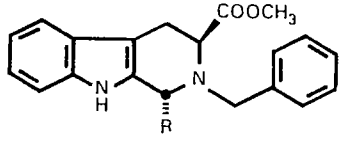
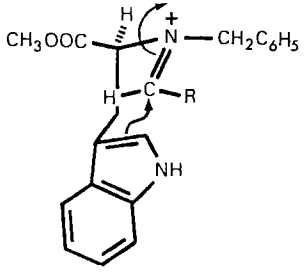
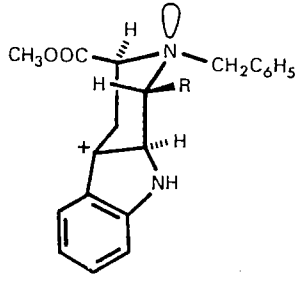


57

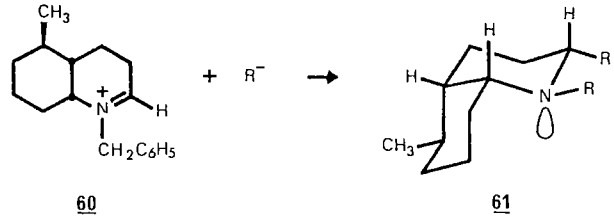


58

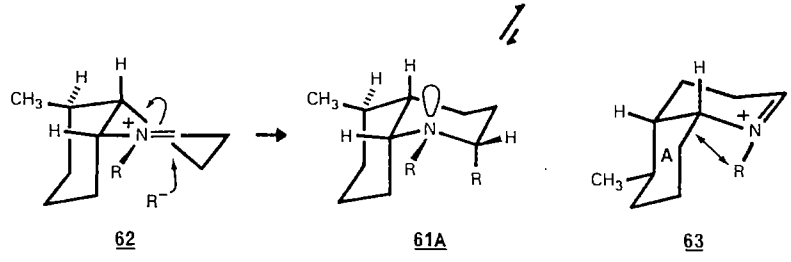


59

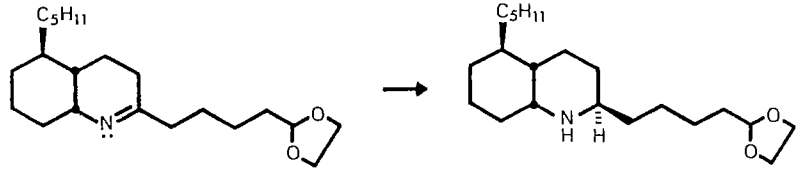
Overman and Fukuya (25) have also observed the unexpected preference of organolithium and Grignard reagents which add to iminium ion 60 from the more sterically congested α face yielding 61. The authors explained their results by a strong stereoelectronic control during the addition of the alkyl group (cf. 62 → 61A → 61). The other conformation 63 was eliminated because of a strong $A^{1,2}$ steric interaction (26) between the N-alkyl group and ring A. Similarly, lithium aluminium hydride reduction of 64 gave 65 as the major isomer (27).



60 61



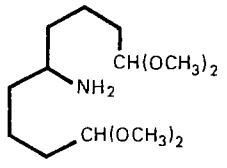
62 61A 63



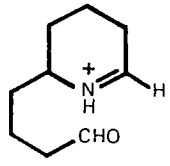
64 65

Stevens and Lee (28) have reported an elegant synthesis of coccinelline (69). Treatment of 66 at pH=1 gave intermediate 67 which was then treated with dimethyl acetone dicarboxylate at pH=5.5 to give a single tricyclic isomer, the ketodiester 68, in 75% yield. Compound 68 was then converted into coccinelline (69). This result shows that the Robinson-Schopf reaction (29, 30) can take place with a remarkable control of stereochemistry.

In principle, there are four possible transition states for the attack of a nucleophile on a cyclic iminium ion such as 67. Two of these, 71 and 72, are boat-like transition states and are kinetically disfavored. Of the two possible chair-like transition states, 70 and 73, the latter suffers from an unfavorable 1,3-diaxial interaction between the R group and the incoming nucleophile. Transition state 70 is therefore favored.



66



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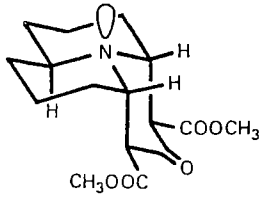
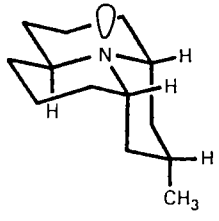


68



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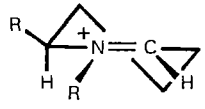
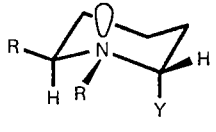


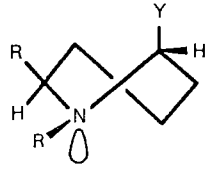
67A

Y⁻

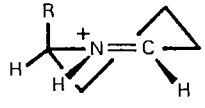


70

Y⁻

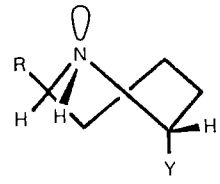


71



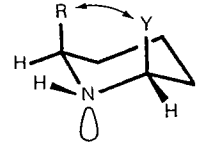
67

Y⁻



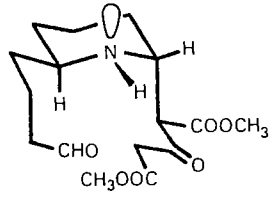
72

Y⁻



73

Consequently, the condensation of 67 with dimethyl acetone dicarboxylate must yield the trans intermediate 74 which after conversion into 75 can be transformed, again with stereoelectronic control, into the cis-trans tricyclic ketodiester 68.



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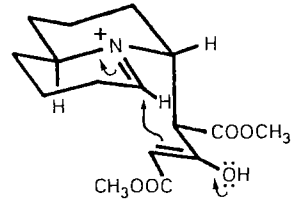

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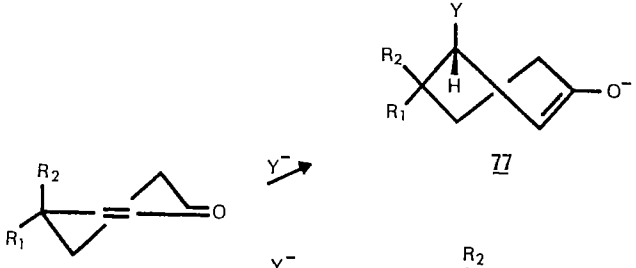
68

α,β-Unsaturated ketones

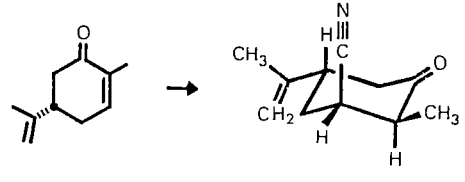
Stereoelectronic effects should also play an important role in the nucleophilic 1,4-additions of anions to conjugated systems. These effects should therefore influence the Michael reaction as well as the hydrocyanation of α,β-unsaturated ketones. Studies on these reactions provided evidence that the kinetically controlled addition of a nucleophile to a cyclohexenone derivative is indeed subject to stereoelectronic effects.

Considering a conformationally rigid cyclohexenone such as 76, an attack by a nucleophile with stereoelectronic control on the top face yields the boat-like enolate ion 77 whereas that on the bottom face gives the chair-like enolate ion 78. The second process should therefore be favored as suggested by Toromanoff (31).

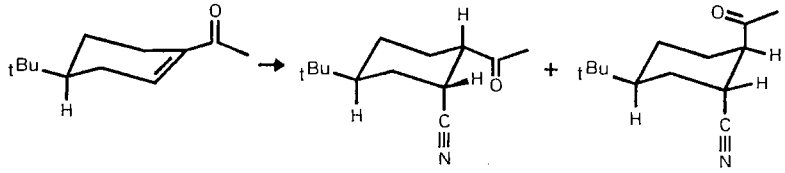


76 77 78

In the conjugate hydrocyanation of (-)-carvone (79), Djerassi and co-workers (32) observed the formation of the axial cyanoepimer 80 as the major product. Similarly, Alexander and Jackson (33) found that substrate 81 gave exclusively the axial cyano compounds 82 and 83. The two epimers 82 and 83 were found to be interconvertible under the reaction conditions. These results indicate clearly that the chair-like enolate process 76 → 78 is the preferred pathway.



79 80



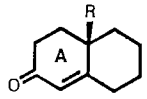
81 82 83

The bicyclic enone 84 in which ring A can adopt the two conformations 85 and 86 can now be examined. A stereoelectronically controlled attack of cyanide ion on the α face of conformation 85 gives the chair-like intermediate 87 while that on the β face of conformation 86 yields the chair-like intermediate 88. An approach from the top face of 85 or the bottom face of 86 is not considered because it leads to intermediates having a boat-like conformation. Intermediate 87 with its trans junction is more stable on the basis of steric effects than intermediate 88 which has a cis ring junction; consequently, the formation of the α-cyano adduct 89 should prevail over the β-cyano adduct 90.

This prediction is supported by several experiments which showed that under kinetically controlled conditions, enones of type 84 give predominantly the α-cyano adduct 89. For a detailed review, the reader is referred to the recent article of Nagata and Yoshioka (34).

Interestingly, the trans enones 91 and 92 (R=H or CH_3) have their ring A essentially conformationally rigid. Consequently, the addition of cyanide ion from the α face, occurring via a chair-like transition state (93 → 94) should be preferred over that on the β face which can take place only via a boat-like transition state (93 → 95). Agami, Fadlallah and Levisalles (35) have recently observed that in strictly kinetically controlled conditions, only the axial cyano isomer resulting from an attack on the α face was observed with the trans enones 91 and 92.

They have further observed that under thermodynamically controlled conditions, the bicyclic α- and β-cyano isomers 96 and 97 can be interconverted to give an equilibrium mixture, and, as predicted on the basis of the stereoelectronic effects, the axial cyano isomer 96 reaches the equilibrium at a much faster rate.



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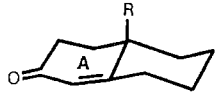

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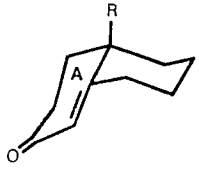

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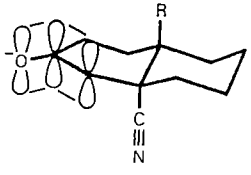

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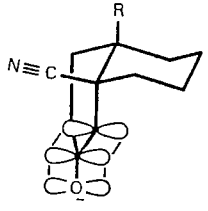

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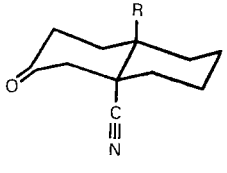

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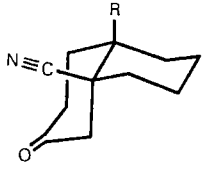

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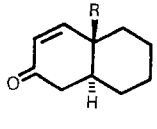

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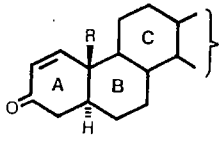

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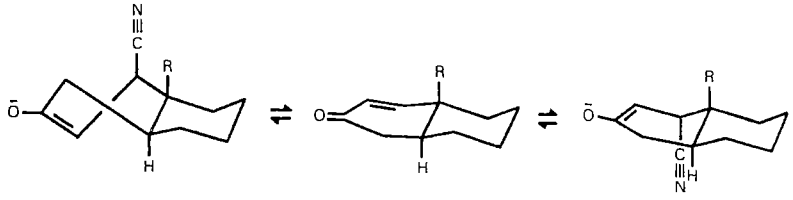
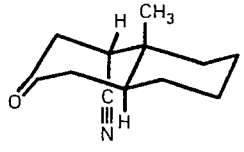


95 93 94



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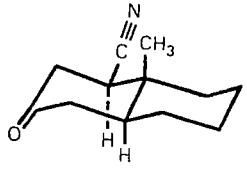
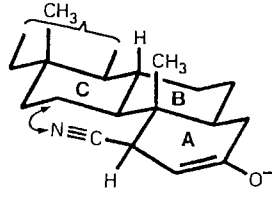


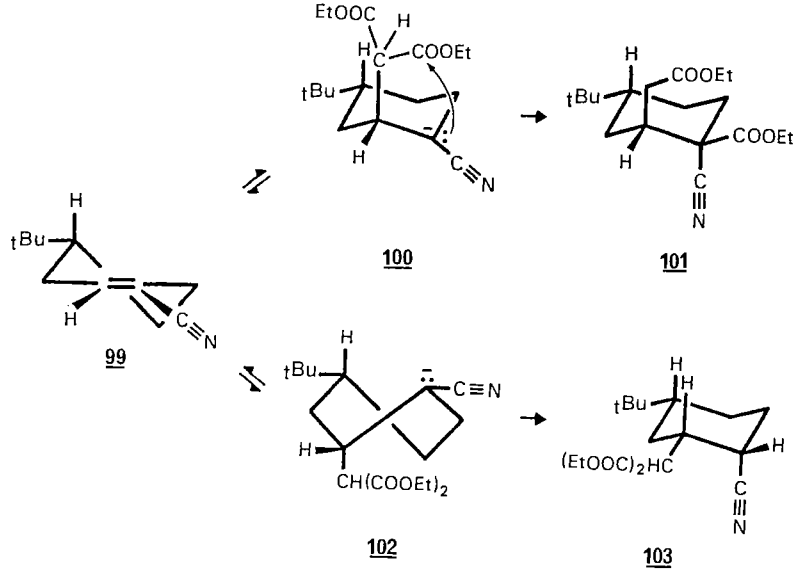
97

Contrary to this bicyclic series, the equilibration of the α- and the β-cyano isomers derived from the steroid enones 92 (R=H or CH_3) does not occur. It has also been impossible to produce the β-cyano isomer from the hydrocyanation reaction. This result was explained by the fact that in the steroid series, there is a strong steric interaction between the cyano group and the C-11 methylene group of ring C in the boat-like conformation 95 (cf. 98). Consequently, addition to the β-face never occurs in these compounds. This was confirmed by the fact that 1α-cyanocholestanone (derived from 92, R=CH_3) readily incorporates labeled cyanide ($^{13}C{\equiv}N$) under the experimental conditions of the hydrocyanation reaction.



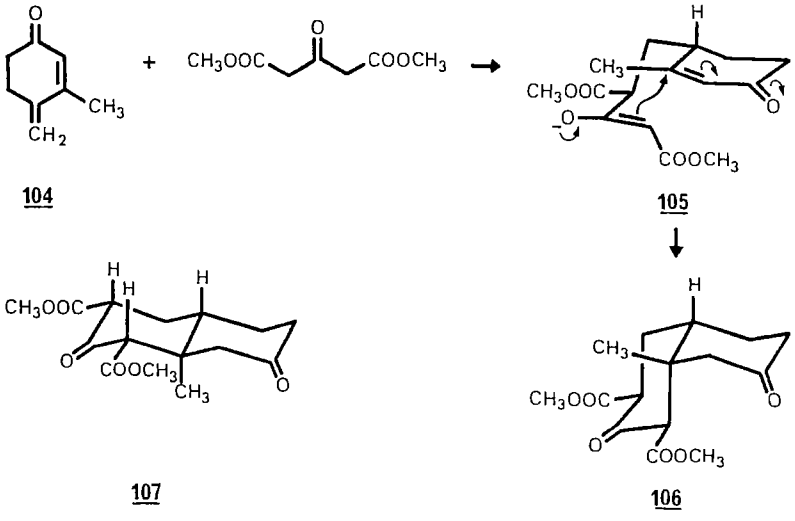
98

Very few studies have been carried out on the stereochemistry of the Michael reaction. However, Abramovitch and Struble (36) have found that compound 101 was the main product when diethyl sodiomalonate (free of ethoxide ion and ethanol) was added to 4-t-butyl-1-cyano cyclohexene (99) in boiling toluene. This result can be rationalized by axial attack on 99 to give first 100 having a chair-like conformation which is then transformed into 101 by internal trapping (see arrow). However, when the addition of diethyl malonate anion was carried out in ethanol under thermodynamically controlled conditions, product 103 with an equatorial malonate group was obtained, presumably via the twist-boat intermediate 102.



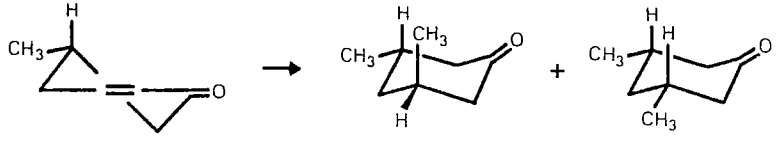
99 100 101 102 103

Irie and co-workers (37) have recently observed that the double Michael reaction of dimethyl acetone dicarboxylate on dienone 104 gave the cis decalin product 106. This result indicates that intermediate 105 underwent a stereoelectronically controlled internal Michael addition to give 106. Without stereoelectronic control in the Michael reaction, there is no apparent reason to prevent the formation of the trans isomer 107. However, if this factor is taken into consideration, examination of molecular models indicates that it seems impossible to obtain isomer 107.



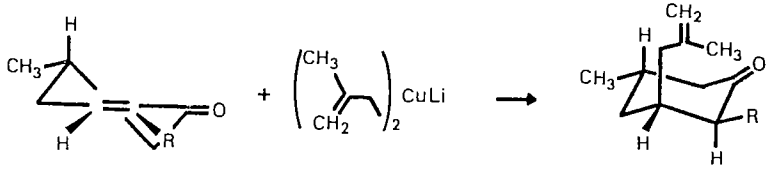
104 105 107 106

House and Fischer (38) have found that lithium dimethyl cuprate reacts with enone 108 and yields a mixture of trans and cis 3,5-dimethyl-cyclohexanones 109 and 110 in a 98:2 ratio. Similar results were observed by Allinger and Riew (39) using methylmagnesium iodide in the presence of copper(I) chloride. In another case, Heathcock and co-workers (40) observed the exclusive formation of the trans isomer 112 from enone 111; no cis isomer was detected. Thus, the preferred mode of approach by cuprate reagent is also 76 → 78 which leads to a chair-like enolate ion.



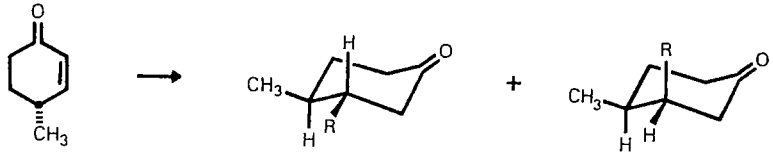
108 109 110

Luong-Thi and Rivière (41) have found that the conjugate addition of organocopper reagents to 4-methyl-2-cyclohexenone (113) gave a mixture of trans and cis cyclohexanones 114 and 115 where the trans isomer largely predominates (≈9:1). Stereoelectronic effects predict that an attack of the most stable conformation of 113 yielding a chair-like intermediate enolate ion should give the cis isomer 115. Predominant formation of the trans isomer is therefore a priori unexpected. It is however possible that the formation



111 112

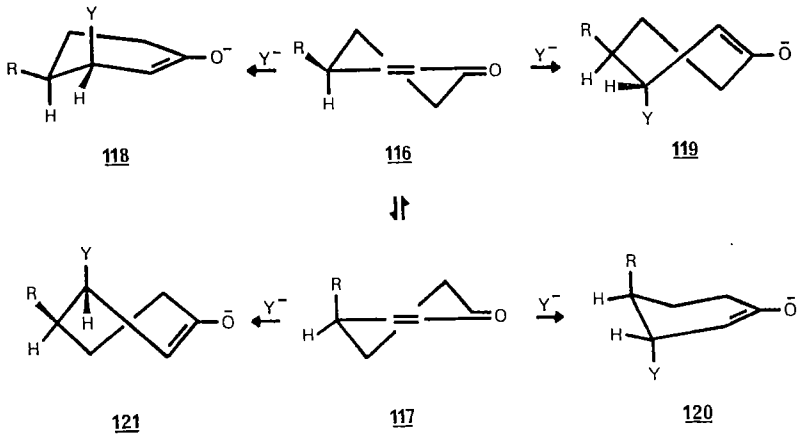
of the cis isomer is suppressed because of a strong steric interaction between the organocopper reagent and the methyl group at C-4 in 113.



113 114 115

Enone 113 can adopt two different conformations 116 and 117. Attack on the top face of the most stable conformation 116 gives the chair-like enolate ion 118 while an attack from below the plane of the molecule yields the boat-like enolate ion 119. On the other hand, an attack on the bottom face of the less stable conformation 117 gives the chair-like intermediate 120 while that on the top face gives the boat-like intermediate 121. The formation of the boat-like 121 where the two groups (R and Y) are cis can be readily eliminated. The chair-like 118 which leads to the cis isomer has to compete with the boat-like 119 and the chair-like 120 which lead to the trans isomer. The possibility of steric hindrance between the incoming nucleophile and the alkyl group at C-4 exists only in the formation of 118. Therefore, this extra steric factor would disfavor the formation of the cis isomer.

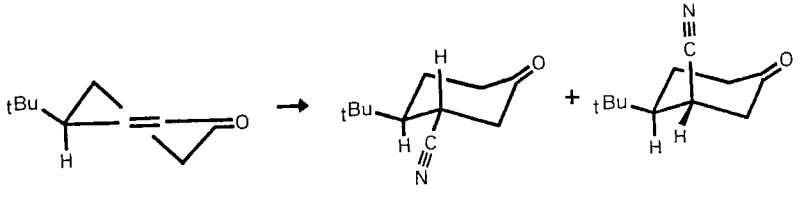
Compelling evidence that this is indeed the correct explanation comes from a study of Rivière and Tostain (42). They have studied the copper-catalyzed methyl Grignard conjugate addition of 4-substituted cyclohexenones and found that when the size of the 4-alkyl group is increased from methyl to isopropyl, the trans:cis ratio varies from 72:28 to 89:11. Also using 113 as a substrate, they found that on increasing the size of the alkyl group of the reagent (RMgX, R=CH_3, C_2H_5 and $(CH_3)_2CH$), the relative percentage of the trans isomer goes from 72 to 88%.



118 116 119

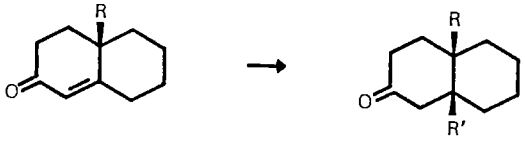
121 117 120

Interestingly, the hydrocyanation of 4-t-butylcyclohexenone gave, as the kinetic product, not the cis (124) but the trans cyanoketone 123. We have seen that there is good evidence that stereoelectronic effects play an important role in the hydrocyanation of conjugated ketones. Consequently, this result can be explained by the above steric argument on the basis of which the formation of the cis isomer 124 is disfavored.



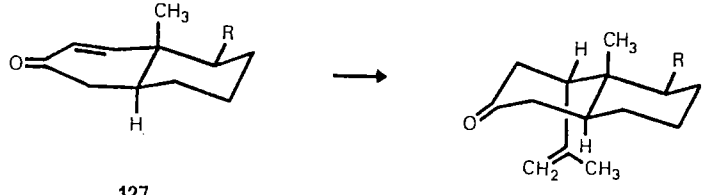
122 123 124

With bicyclic enones such as 125, conjugate addition of organocopper reagents gives mainly the corresponding cis decalin product 126, as described in the review by Posner (43). We have already seen that in this type of bicyclic enone, ring A can take two different conformations (cf. 85 and 86 in p. 224) which can give either a trans (from 85) or a cis (from 86) product with stereoelectronic control. With simple nucleophiles, the trans isomer was always favored. The opposite result obtained with organocopper reagents indicates that there are other factors which favor the transition 86 → 88 (CN=R) over the transition 85 → 87 (CN=R).



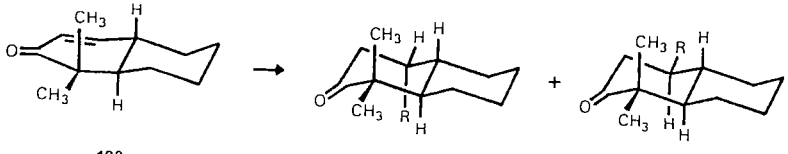
125 126

Piers and co-workers (44) have reported that the cuprous chloride catalyzed 1,4-addition of isopropenylmagnesium bromide to the bicyclic enones 127 (R=H or CH_3) gave exclusively the bicyclic ketones 128 (R=H or CH_3) with the isopropenyl group axially oriented. Interestingly, with their trans A/B ring junction, these enones are essentially conformationally rigid and their reactivity is in accord with the predictions made on the basis of stereoelectronic effects.

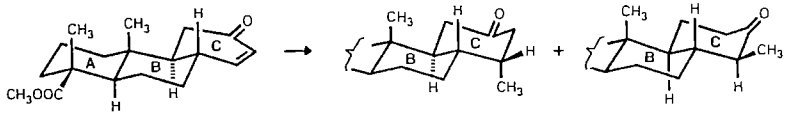


127 128

However, the α,α'-dimethyloctalone 129 and the tricyclic enone 132 behaved differently. Marshall and Andersen (45) obtained from 129 a mixture of isomers 130 and 131 (54% axial and 46% equatorial, when R=isopropyl and 82% axial and 17% equatorial when R=methyl) while Spencer and collaborators (46) isolated a ≈1:1 mixture of 133 and 134 from 132. By comparison with enones 127 which have an angular methyl group, the replacement of that group for a hydrogen atom in 129 and 132 must have eased the approach of the reagent on the top face to give products 131 and 134 with the equatorial alkyl group via a boat-like transition state.

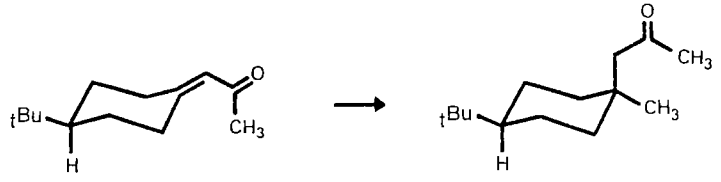


129 130 131



132 133 134

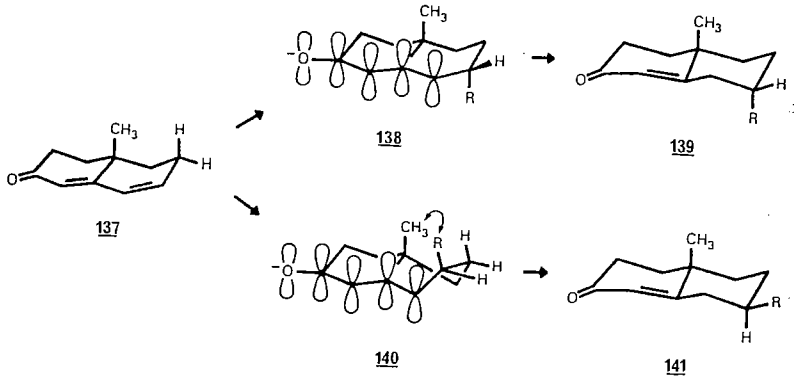
A report of House, Respess and Whitesides (47) showed that the reaction of lithium dimethyl cuprate with the unsaturated ketone 135 gave exclusively the ketone 136 having the methyl trans to the t-butyl group. In this case where the double-bond is exocyclic, stereoelectronic effects allow equal attack from either face. Thus, the exclusive formation of 136 must be due to steric reasons only, the equatorial approach being favored.



135 136

In conclusion, in the case of 1,4-conjugated additions to α,β-unsaturated ketones, some substrates, in order to avoid steric interaction, react through a boat conformation to give an equatorially substituted product, but when there is no steric interaction, the axial attack through a chair conformation is energetically favored. Both processes are however stereoelectronically controlled.

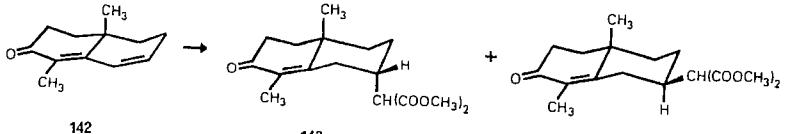
The 1,6-addition to α,β,γ,δ-dienones is also subject to stereoelectronic effects. Addition on the bottom face of dienone 137 leads to a chair-like intermediate 138 while that on the top face leads to a boat-like intermediate 140 in order to maintain maximum orbital overlap. Also, in 140 the R group encounters an eclipsed 1,2-R/H interaction and more importantly, a 1,4-CH_3/R steric interaction which resembles the bowsprit flagpole arrangement of a twist-boat form of cyclohexane. This analysis of Marshall and Roebke (48) predicts that the trans product 139 should prevail over the cis product 141.



137 138 139 140 141

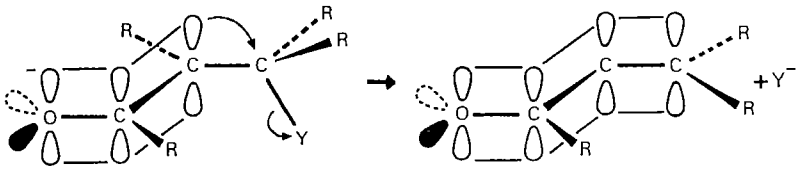
Support for this view comes from their work on the stereochemistry of 1,6-addition (catalyzed by cupric acetate) of methyl-, ethyl-, isopropyl-, and t-butylmagnesium halides on dienone 137: 93% of the axial isomer 139 was obtained with CH_3MgI, 98% with C_2H_5MgBr and 100% with $(CH_3)_2CHMgBr$ and $(CH_3)_3CMgCl$. Campbell and Babcock (49) have also studied the cuprous catalyzed reaction of methylmagnesium iodide with various steroidal 4,6-dien-3-ones. They found axially substituted C-7 methyl derivatives as the predominant 1,6-adducts.

When the bicyclic dienone 142 was treated with dimethyl malonate and potassium t-butoxide in t-butanol at 25°C for 10 days, the axial isomer 143 was obtained in 51% yield. None of the equatorial isomer 144 was isolated. When the reaction was carried out at reflux, a mixture of 143 and 144 was isolated in which the more stable equatorial isomer predominated (50).



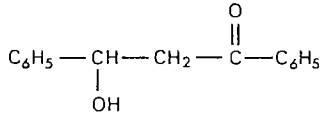
142 143 144

We have already seen evidence from the retrohydrocyanation reaction (p. 222) that the ejection of a leaving group β to a carbonyl which yields an α,β-unsaturated system should also be stereoelectronically controlled, i.e. the C — Y bond of the leaving group should be parallel to the π system of the enolate ion (145 → 146).



145 146

Further evidence that this is indeed the case comes from the dehydration under basic conditions of β-hydroxy ketones (51-54). For example, the dehydration of 147 can yield the cis or the trans conjugated ketones 149 and 151 via the enolate anions 148 and 150 respectively. The formation of the trans product 151 is favored because there is less steric interaction between the planar enolate anion system and the phenyl group at the β-carbon



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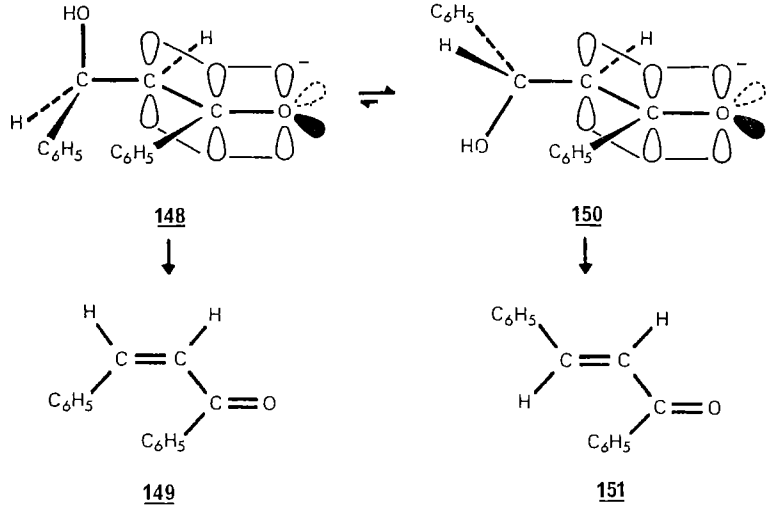
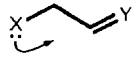


148 150 149 151

in the conformation 150. In other words, in the transition state leading to the trans product, the two large phenyl groups are not eclipsed. It is therefore a combination of steric and stereoelectronic effects which control this reaction.

The rules of Baldwin (55) for ring closure in trigonal systems (see p. 171 for an introduction) are the following: 3- to 7-Exo-Trig processes (152-156) are all favored processes. 3- to 5-Endo-Trig (157-159) are disfavored but 6- and 7-Endo-Trig (160-161) are favored. The literature is replete with examples of 3- to 7-Exo-Trig: for instance, lactonization of ω-hydroxy-acids and esters are of this type, the formation of lactams from ω-aminoacids and also the Dieckmann cyclization of diesters.



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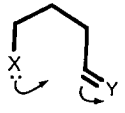

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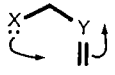

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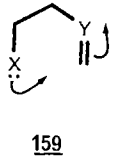

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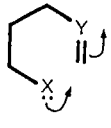

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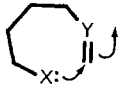
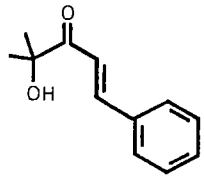


161

Baldwin and co-workers (56, 57) have reported that all attempts to cyclize hydroxy-enones 162 and 164 (R=H or OCH_3) under basic conditions failed to give the corresponding furanones 163 and 165 (R=H or OCH_3). The susceptibility of these systems to conjugate addition of alkoxide nucleophile was verified by conducting the attempted cyclization with sodium methoxide in deuterated methanol. Under these reaction conditions, the α-deuterated analogs (cf. 166) of 162 and 164 (R=OCH_3) were isolated. The incorporation of a deuterium atom α to the carbonyl group was rationalized as a consequence of reversible addition of the methoxide anion giving an adduct such as 167 which underwent deuterium exchange and subsequent elimination of methanol.



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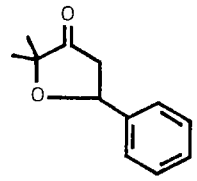

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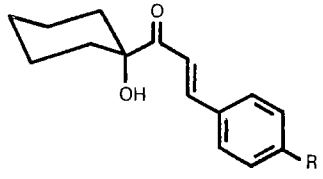

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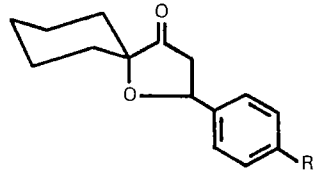

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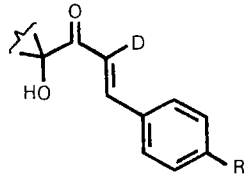

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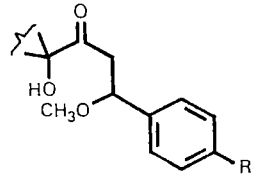
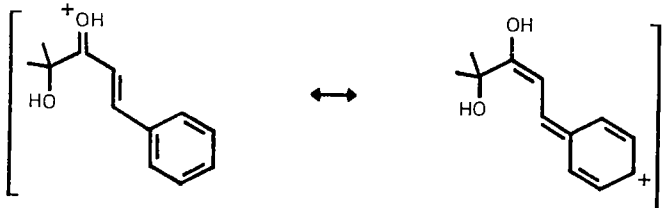


167

On the other hand, they have shown that furanones 163 and 165 (R=H or OCH_3) rapidly and efficiently exchange both their α-hydrogen atoms under the same basic conditions in which 162 and 164 are not converted into 163 and 165. This proves that the lack of ring closure or ring opening is a result of a kinetic rather than a thermodynamic barrier. Thus, the 5-Endo-Trigonal process (159) is indeed a geometrically disfavored reaction.

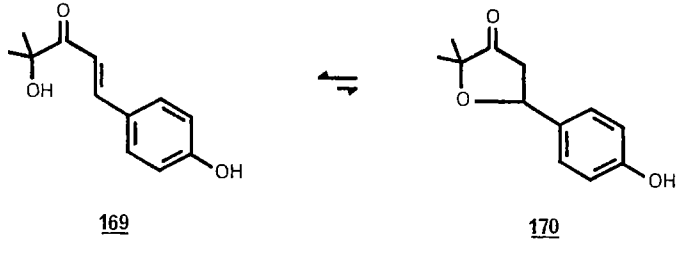
The acid-catalyzed cyclization of hydroxy-enones 162 and 164 (R=H or OCH_3) gives the corresponding furanones 163 and 165. The success of these reac-

tions is attributed to the reduction in the rotational barrier around the enone double-bond, (cf. 168A and 168B), allowing thereby a cyclization (the closure of 168B is a 5-Exo-Trig allowed process).

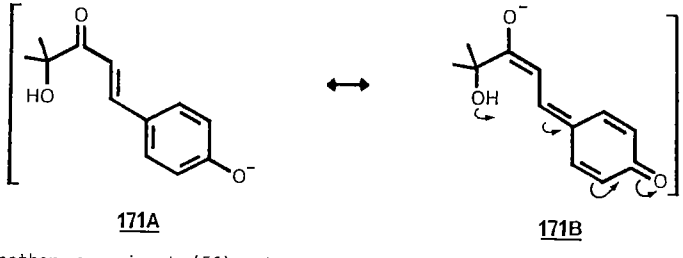


168A 168B

The phenolic enone 169 was recovered unchanged from treatment with sodium methoxide; however, treatment of furanone 170 under the same basic conditions gave smoothly the enone isomer 169. Therefore, the lack of closure of 169 is the result of an unfavorable equilibrium. The process 170 → 169 can be looked at as a 5-Exo-Trigonal process due to the resonance structure 171B.



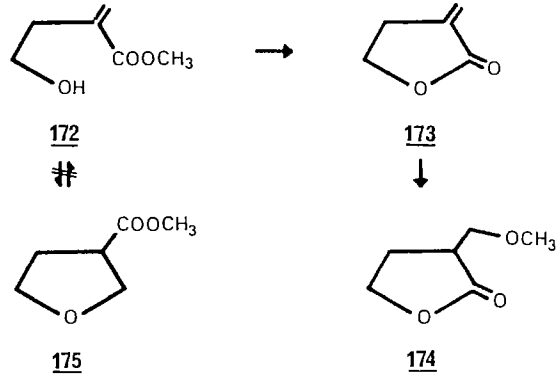
169 170



171A 171B

In another experiment (56), the disfavored 5-Endo-Trig process (159) was placed in competition with the favored 5-Exo-Trig process (154). The hydroxy conjugated ester 172 upon treatment with a variety of bases closed efficiently and cleanly to the lactone 173 (5-Exo-Trig process) with no trace

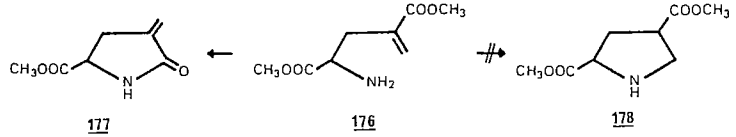
of tetrahydrofuran 175 (5-Endo-Trig process). Also, 173 smoothly added methoxide ion to yield the ether 174, showing that the double-bond is very susceptible to Michael type addition. Again, the ester 175 exchanged its α-hydrogen atom under the conditions of conversion of 172 to 174 with no reversion to 172.



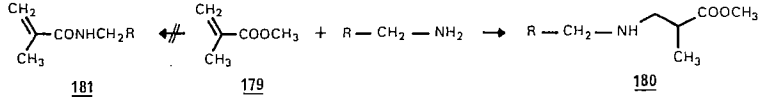
172 173

175 174

A nitrogen analog of 172 was also studied (56). The amino-diester 176, upon release from its stable hydrochloride salt, rapidly closed at 25°C to the lactam 177 (100%) via the favored 5-Exo-Trig pathway. The disfavored 5-Endo-Trig process yielding the cyclic amino-diester 178 was not observed. On the other hand, it is known that primary amines undergo a 1,4-addition to α-substituted acrylic esters (179 → 180) more rapidly than they are acylated to the α-substituted acrylamides (179 → 181).



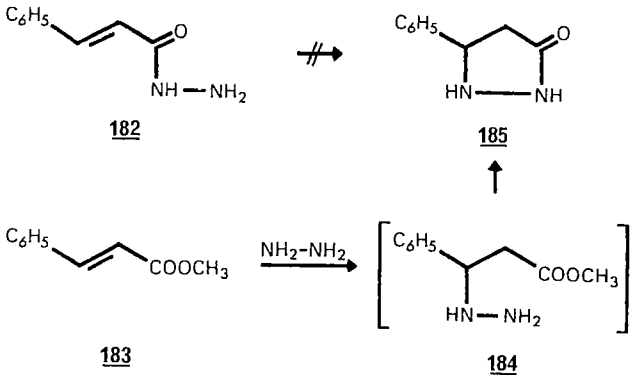
177 176 178



181 179 180

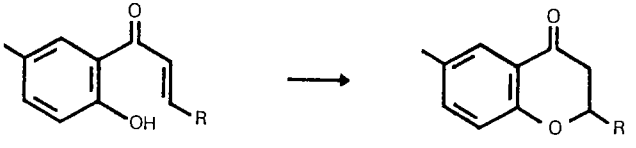
The reactions of cinnamic acid derivatives with hydrazine are also in accord (56) with the above findings. The hydrazide 182 cannot, even at 200°C, be converted into the pyrazolone 185 (5-Endo-Trig process). However, the ester

reacts with hydrazine at 65°C to give cleanly 185, by way of the 1,4-adduct 184, followed by the favored 5-Exo-Trig closure.



182 185 183 184

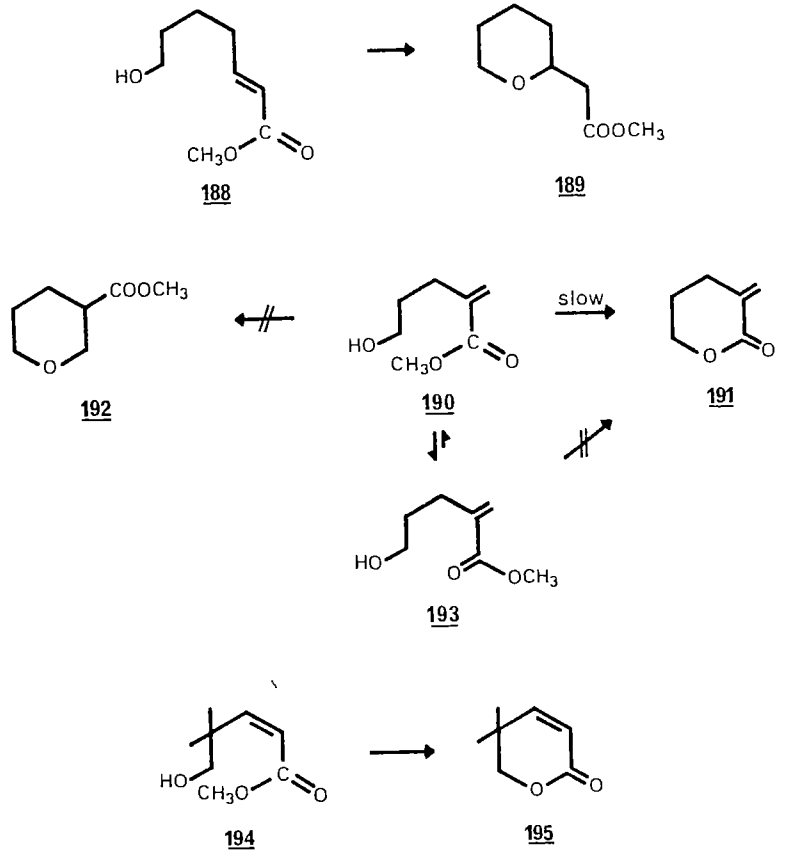
In contrast, to the difficulty of ring closure by the 5-Endo-Trig pathways, the 6-Endo-Trig reaction occurs readily: on treatment with methanolic sodium methoxide the α,β-unsaturated ketones 186 smoothly closed to the 4-chromanones (187) (56).



186 187

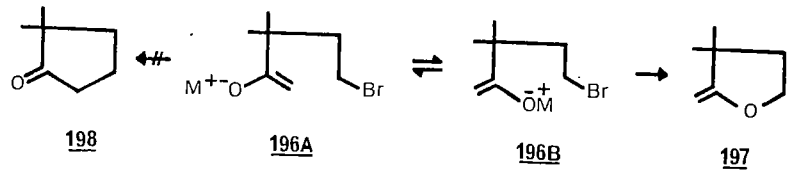
The 6-Exo-Trigonal (155) and the 6-Endo-Trigonal (160) processes are favored for the formation of six-membered rings. However, when a choice of these two modes of ring closure exists, the Exo pathway is the faster ring closing process as shown by Baldwin and Reiss (58). Treatment of trans-heptenoate ester 188 with a variety of bases (NaH, CH_3ONa, t-BuOK) led rapidly to the cyclic tetrahydropyran 189 in quantitative yield via the 6-Exo-Trig pathway. In contrast, the ester 190 cyclized relatively slowly under the same conditions to the α-methylene lactone 191 and gave none of the product of the 6-Endo-Trig mode, i.e. the tetrahydropyran 192. Also, 192 was found readily to exchange the proton α to the ester function under the cyclization conditions of 190 to 191. The relatively slower formation of 191 was attributed to the fact that the starting product exists in the preferred S-Trans con-

formation 193 (rather than the S-Cis 190) in which the 6-Exo-Trig closure is sterically improbable. This is in contrast with the extremely rapid closure of the ester 194 to the lactone 195 (a 6-Exo-Trig process) even under neutral conditions.

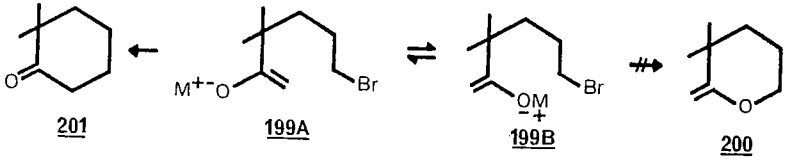


188 189 192 190 191 193 194 195

Baldwin and Kruse (57) have found that the enolate salts 196A-B (M=Li or K) give the enol-ether 197 and no cyclopentanone 198. In contrast to this result, the enolates 199A-B (M=Li or K) under the same conditions gave only the cyclohexanone 201. In this case, the enol-ether 200 was not formed.



198 196A 196B 197

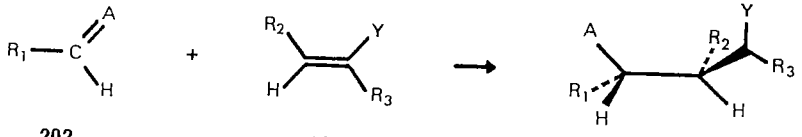


201 199A 199B 200

Baldwin concluded that the remarkable difference between these two cyclizations results from stereoelectronic control of the alkylation of the ambident nucleophile, i.e. the enolate ion. For such an ion, carbon alkylation requires approach of the electrophile perpendicular to the plane of the enolate, whereas oxygen alkylation requires approach in the plane of the enolate. Consequently, in the five-membered ring case, the C-alkylation process 196A → 198 (which can be considered as a 5-Endo-trigonal process) is sterically difficult, but not the O-alkylation process 196B → 197 (a 5-Exo-tetrahedral process).

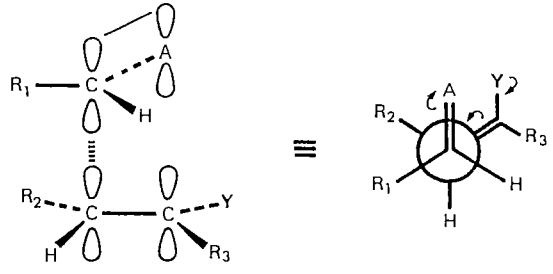
In a very recent paper, Seebach and Golinski (59) have proposed a series of rules which explain the preferred formation of the threo-configuration 204 in the condensation of the Michael acceptor 202 with the Michael donor 203. These are:

(a) staggering of all bonds around the newly formed bond is necessary,
(b) the C=C ond of the donor must be in a gauche (synclinal) arrangement between the C=A and the C−H bond of the acceptor,
(c) the H-atom, the smaller substituent on the donor component, must be in an anti (antiperiplanar) position with respect to the C=A bond.

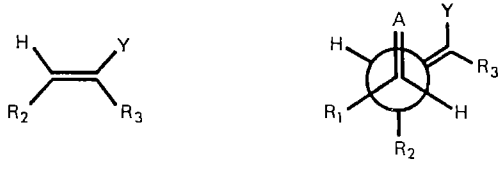


202 203 204

Therefore, the preferred approach of the two components is illustrated by 205 (or by the Newman projection 206). When the donor has the geometry 207, the actual donor and acceptor groups are again situated close to each other (cf. 208).

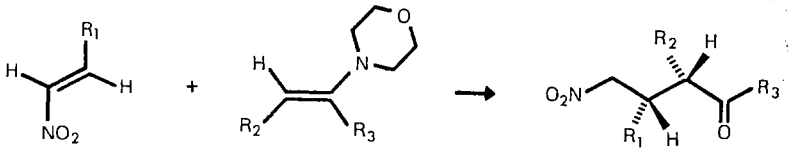


205 206



207 208

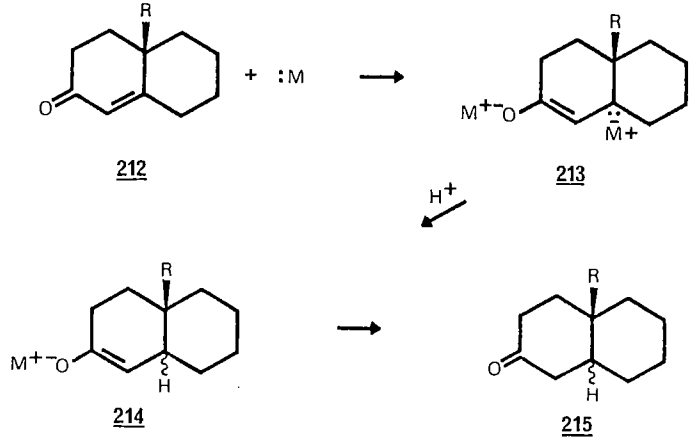
This topological rule readily explained the reaction product 211 (>90% stereoselectivity) of open-chain nitroolefins 209 with open-chain enamines 210. Seebach and Golinski have further pointed out that several condensation reactions can also be rationalized by using this approach: (a) cyclopropane formation from olefin and carbene, (b) Wittig reaction with aldehydes yielding cis olefins, (c) trans-dialkyl oxirane from alkylidene triphenylarsane and aldehydes, (d) ketenes and cyclopentadiene 2+2-addition, (e) (E)-silylnitronate and aldehydes, (f) syn and anti-Li and B-enolates of ketones, esters, amides and aldehydes, (g) Z-allylboranes and aldehydes, (h) E-alkylborane or E-allylchromium derivatives and aldehydes, (i) enamine from cyclohexanone and cinnamic aldehyde, (j) E-enamines and E-nitroolefins and finally, (k) enamines from cycloalkanones and styryl sulfone.



209 210 211

Reduction of α-β-unsaturated carbonyl compounds

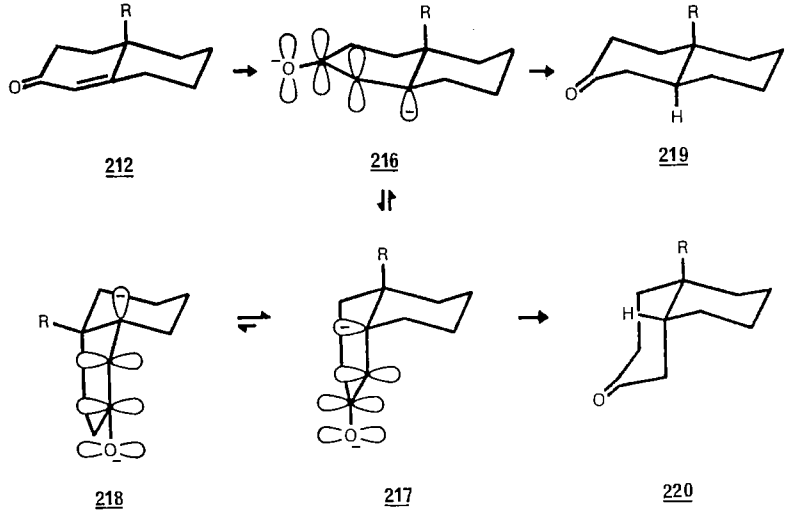
The mechanism of the chemical reduction of enones with metal (Li, Na, etc.) in liquid ammonia can be described by the following equation in which the substrate 212 receives two electrons from the metal to give the dianion intermediate 213. This intermediate is then successively transformed into the enolate salt 214 and the ketone 215 with an appropriate proton donor source. It can readily be seen that the stereochemical outcome of this reaction depends on the stereochemistry of the protonation step 213 → 214. An excellent review on this topic has been recently written by Caine (60). This subject will be only briefly discussed here.



212 213 214 215

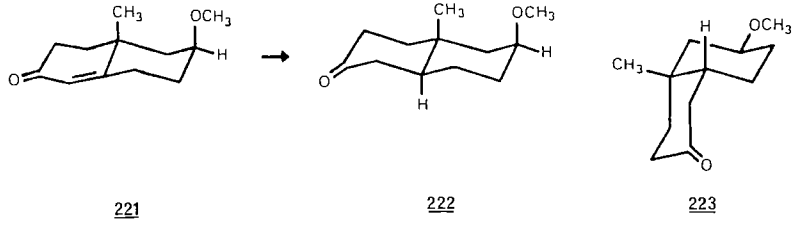
In the reduction of octalone of the type 212, the resulting enolate dianion 213 can adopt three different half-chair conformations 216, 217, and 218. Of these, only conformations 216 and 217 have the carbanion electron pair parallel to the π orbital of the enolate system allowing an electronic de-

localization. Thus, product would come from the protonation of 216 from the bottom face yielding the trans bicyclic ketone 219 or from the protonation of 217 from the top face yielding the cis product 220. In simple cases, the conformer 216 is more stable than 217 (less steric interaction); the formation of the trans product 219 usually predominates.



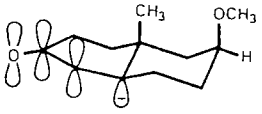
212 216 219 218 217 220

The above stereoelectronic arguments were proposed by Stork and Darling (61) to explain why the more stable isomer is not necessarily always obtained (62). For example, reduction of the octalone 221 with lithium-ammonia-ethanol followed by oxidation afforded the trans-2-decalone 222 even though the isomeric cis-2-decalone 223 is about 2 kcal/mol more stable than 222. Conformation 226 of the enolate dianion is the most favored sterically but it is electronically disfavored. Conformations 224 and 225 are both electronically favored but 225 is less favored sterically than 224. Therefore,



221 222 223

the enolate dianion intermediate should exist in conformation 224 which is then protonated to give the trans-product 222.



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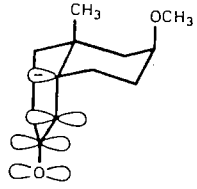

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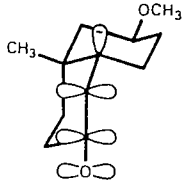
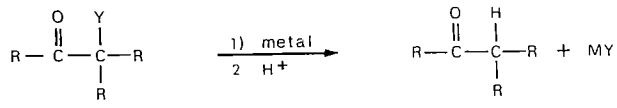


226

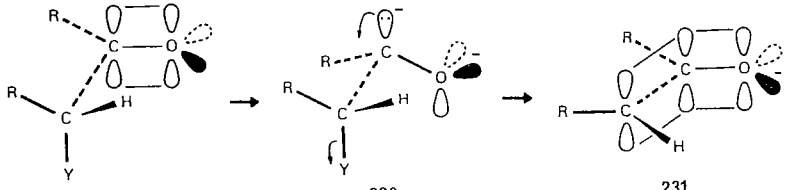
The reduction of 212 (R=H) gives a mixture of trans and cis decalones 219 and 220 (R=H) in a 99:1 ratio (63). An analysis of non-bonded interactions in the corresponding enolates 216 and 217 (R=H) indicates that the former should be favored only by about 1.0 kcal/mol, which should correspond to an approximately 80/20 trans/cis ratio. This result indicates that there is a significantly greater preference for the trans species 216 than would be predicted by analysis of non-bonded interactions.

Other factors (charge repulsion, solvation factors, etc.) could influence the position of the equilibrium in favor of enolate dianion 216. It is also possible that there is a kinetic preference for the formation of dianion 216 and that this species would undergo protonation more rapidly than equilibration. This rule of "axial protonation" of 216 has been found to be widely applicable in many cases. However, in systems in which a significant amount of strain must be introduced in order for protonation to occur axially on 216, protonation of conformer 217 (and even conformer 218) becomes important (60).

The hydrogenolysis reaction of α-halo (Y=halogen), α-amino ($Y=NR_2$), α-acyloxy (Y=OCOR) and α-hydroxy (Y=OH) ketones 227 with metals (Li, Ca, Zn, etc.) (64, 65) to yield the corresponding ketone 228 must also be strongly influenced by stereoelectronic effects (66). House (67) has pointed out that it is probably necessary that the α-substituent Y must be able to occupy a conformation in which the π system of the carbonyl group is parallel to the C — Y bond (229). In such a conformation, the carbonyl group can accept two electrons to give 230 which can easily eject the Y^- group, generating in this way the intermediate enolate ion 231.

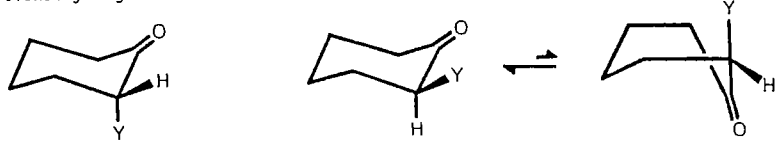


227 228



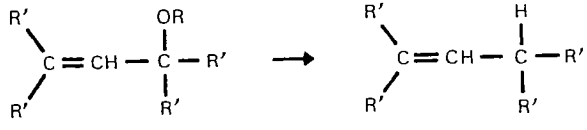
229 230 231

It follows that a conformationally rigid cyclohexanone with a Y group axially oriented should react in its ground state conformation 232 while that with the Y group equatorially oriented (233) should react via its boat conformation (234). As a consequence, cyclohexanones with axial alpha substituents must be reduced more readily than analogous compounds with equatorial substituents, especially when the two compounds are essentially conformationally rigid (68).



232 233 234

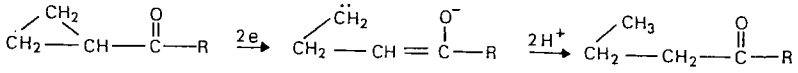
The hydrogenolysis of allylic ether and acetate (235 → 236, R=alkyl or $COCH_3$) should also take place more easily when the compound can adopt a conformation in which the OR group can become parallel to the π orbital of the double bond (69). The same stereochemical requirement must also be necessary in the hydrogenolysis of a substituent in a benzylic position (70).



235 236

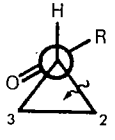
Reduction of cyclopropyl ketone

The reductive opening of a cyclopropane ring of a conjugated cyclopropyl ketone with lithium in liquid ammonia can be viewed as an overall two electrons reduction which yields the equivalent of a carbanion and an enolate ion (cf. 237). Successive protonations of 237 then gives the reduced ketone.

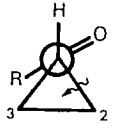


237

Norin (71) and Dauben and collaborators (72-74) have shown that the bond of the cyclopropane ring which is reductively cleaved corresponds to the bond which better overlaps with the π system of the adjacent carbonyl group. Thus, when the cyclopropyl ketone exists preferentially in the cisoïd and transoïd conformations described by the Newman projections 238 and 239, the C_1-C_2 bond is always cleaved in preference to the C_1-C_3 bond.

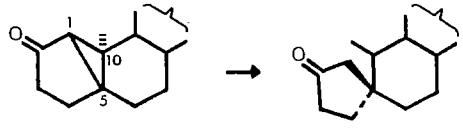


238

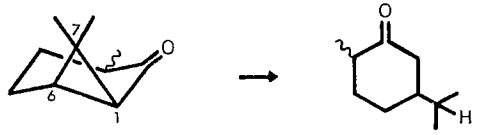


239

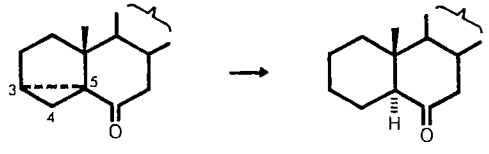
A few representative examples will be reported here. The reduction of lumicholesterone (240) with lithium in liquid ammonia gives the spiroketone 241 in high yield (70). Thus, the C_1-C_{10} bond which better overlaps with the π system of the carbonyl groups is cleaved. Norin (71) as well as Dauben and Deviny (72) have reported the reduction of (±)-carone (242) into 243. In this case, the C_1-C_7 bond was cleaved for the same stereoelectronic reason. The isomeric 3α,5- and 3β,5-cyclocholestan-6-ones 244 and 246 gave respectively cholestan-6-one (245) and 3α-methyl-5,β-A-norcholestan-6-one (247). Examination of models clearly showed that in the 3α-5 isomer 244, the C_3-C_5 bond, and in the 3β-5 isomer 246, the C_4-C_5 bond were the better overlapping bonds. The isomeric 4,5-methano steroids 248 and 250 were also studied and the same arguments for the direction of cleavage as mentioned for carone can be applied here. Both materials upon reaction with lithium in liquid ammonia give in high yield a single product 249 and 251 respectively.



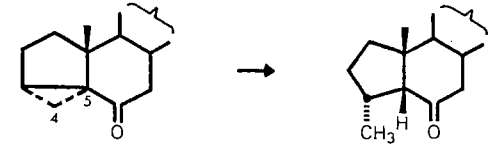
240 241



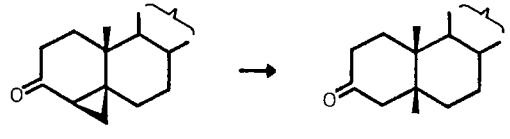
242 243



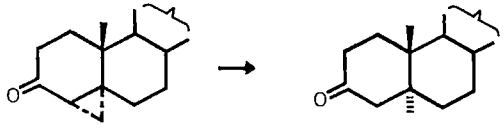
244 245



246 247

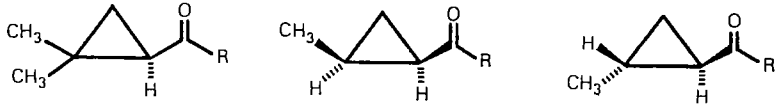


248 249



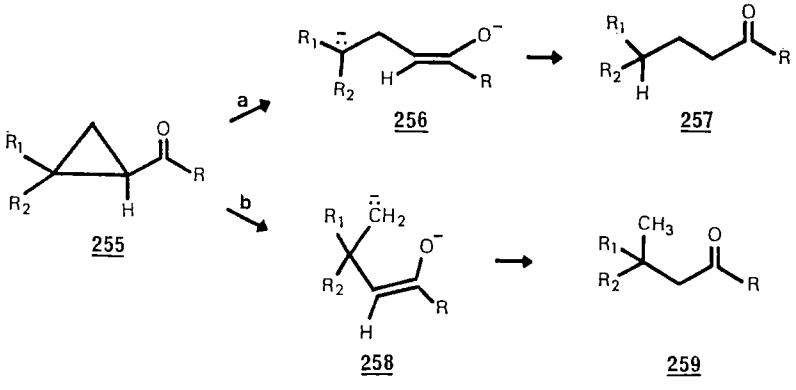
250 251

Dauben and Wolf (73) have also studied the chemical reduction of a series of acyclic cyclopropyl ketones (252-254) with lithium in liquid ammonia.



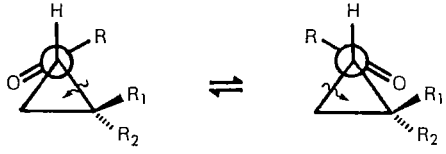
252 253 254

These compounds can give two different types of products (path a: 255 → 256 → 257 and path b: 255 → 258 → 259).



The preferential formation of either 257 or 259 can be rationalized via a specific cleavage of the cyclopropyl C—C bond which has maximum overlap with the carbonyl group in the conformation which has the least steric interactions.

The cisoïd conformation (cf. 238) is more reactive than transoïd conformation (cf. 239) (vide infra), so we will consider only the cisoïd conformations 260 and 261 for compounds having the general structure 255. Reductive cleavage of conformations 260 and 261 must give respectively compound 257 (via path a) and compound 259 (via path b).

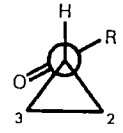


260 261

The dimethylketone 252 must exist preferentially in conformation 260 (R_1=R_2=CH_3) which has much less steric interaction than conformation 261 (R_1=R_2=CH_3). The reduction of 252 must therefore give mainly compound 257 via path a. Experimentally, an 8:2 ratio of 257 and 259 (R_1=R_2=CH_3) was indeed obtained. The cis ketone 263 must also exist preferentially in conformation 260 (R_1=CH_3; R_2=H), so, product 257 via path a should be formed predominantly. This was confirmed experimentally as a 9:1 mixture of 257 and 259 (R_1=CH_3, R_2=H) was formed. The trans ketone 254 must exist as an approximately equal mixture of conformations 260 and 261 (R_1=H, R_2=CH_3) so, an equal proportion of products from path a and path b should be expected. Experimentally, it was found that path b is preferred in a 9:1 ratio. The preferred formation of 259 (R_1=CH_3, R=H) could be explained because path b yields intermediate 258 (R_1=H, R_2=CH_3), a primary carbanion which is more stable than the secondary carbanion 256 (R_1=H, R_2=CH_3).

In another investigation, Dauben and Wolf (74) have shown that the cisoïd conformation 238 is reduced in preference to the transoïd conformation 239. This was proven by trapping the enolate ion intermediate with acetic anhydride. Reduction of the cisoïd conformation 238 yields an enolate dianion which is protonated by ammonia to give the trans enolate ion 262. This ion is then trapped by acetic anhydride to yield the trans enolacetate 263. Similarly, the transoïd conformation 239 must give the cis enolacetate 265 via the cis enolate ion 264. The compounds chosen for this study were 266, 267, and 268. Accordingly, the experimental results gave a trans:cis ratio for the corresponding enolacetates of 82:18, 88:12, and 70:30 respectively.

It is also possible to reductively cleave a C—C bond (which is not part of a cyclopropane ring) when this bond is parallel to the π system of two adjacent carbonyl groups. The pentacyclic diketone 269 is a perfect example for this stereochemical arrangement and Wenkert and Yoder (75) found that 269 is readily reduced to the tetracyclic diketone 270 with zinc in acetic acid. Paquette and co-workers have reported the transformations 271 → 272



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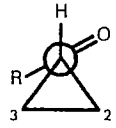

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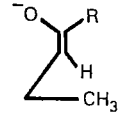

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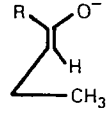

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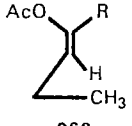

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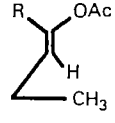

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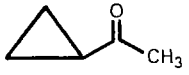

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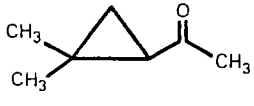

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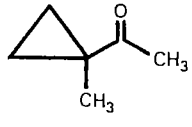
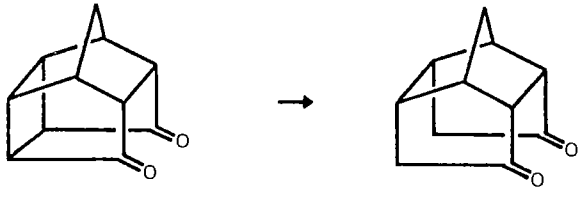
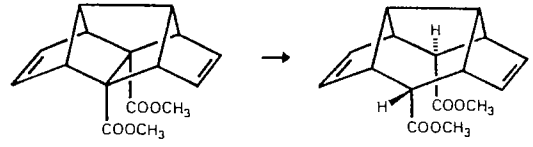


268

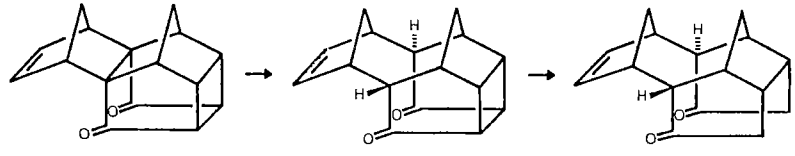
(Na, NH_3) (76) and the two consecutive ring cleavages 273 → 274 → 275 using zinc (77, see 78, 79 for other similar transformations).



269 270

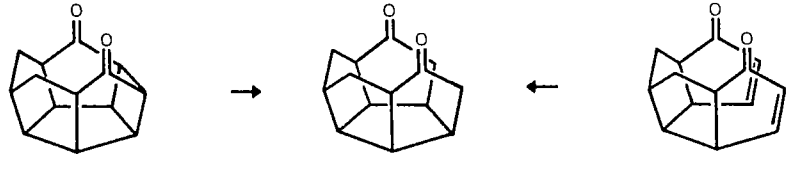


271 272



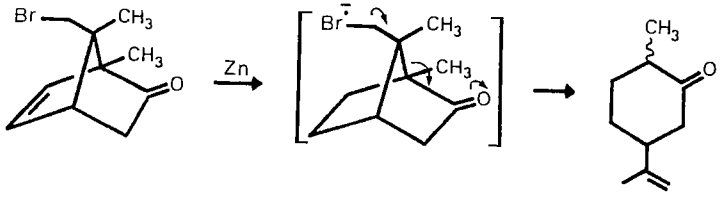
273 274 275

A similar C — C bond cleavage 276 → 278 (using zinc) has been observed by Eaton and co-workers (80). However, what is more interesting is that compound 278 can be produced directly from the bis-enone 277 upon treatment with zinc. This unusual reaction was successful because the π systems of the two double-bonds are perfectly oriented to induce the C—C bond formation.

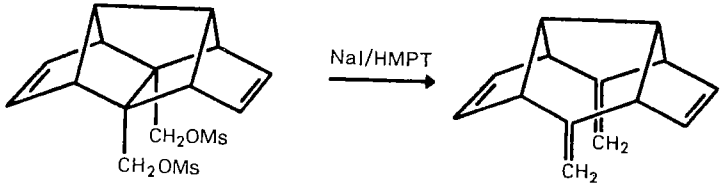


276 278 277

Reductive cleavages of C — C bonds can also take place when one and even the two carbonyl groups are replaced by other easily reduced functional groups. The only requirement appears to be the proper syn- or antiperiplanar orientation of the reacting functional groups with the C — C bond to be cleaved. The following transformations 279 → 280 and 281 → 282 reported by Baker and Davis (81) and Paquette and Wyvratt (82) respectively constitute representative cases.



279 280



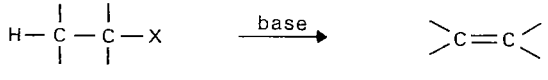
281 282

DOUBLE-BOND FORMATION

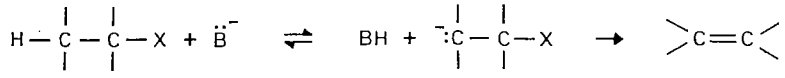
E2 and ElcB

We have previously discussed (Chapter 5) that the formation of a double-bond from a carbonium ion requires that the bond to the hydrogen on the adjacent carbon should be parallel to the p-orbital of the positively charged carbon atom. This topic will not be further discussed in this Chapter which is concerned with double-bond formation under basic conditions.

In principle, stereoelectronic effects should play an important role in the formation of double-bonds in base-promoted eliminations of HX.

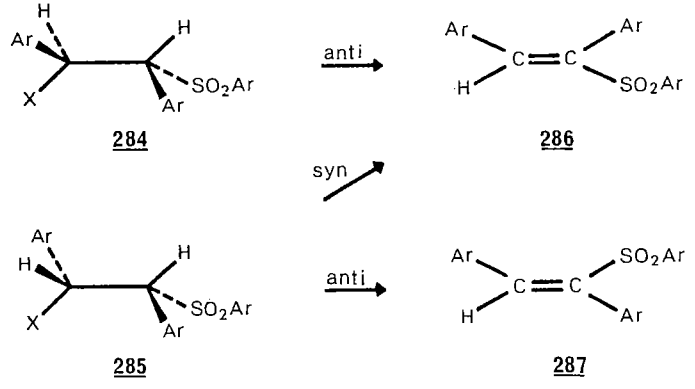


This reaction can take place by either a step-wise or a concerted mechanism. In the non-concerted mechanism (ElcB), the C−H bond is ruptured prior to the scission of the C−X bond. Thus, strong stereoelectronic effects should be observed depending on the relative orientation of the electron pair and the C−X bond in 283; indeed, when the electron pair is oriented antiperiplanar to the C−X bond, it should ease the formation of the double-bond.



283

A great deal of experimental results have been rationalized on that basis; for instance, compound 284 gives only the olefin 286 via an anti process while the isomer 285 gave a mixture of olefin 286 (syn mode) and 287 (anti mode).



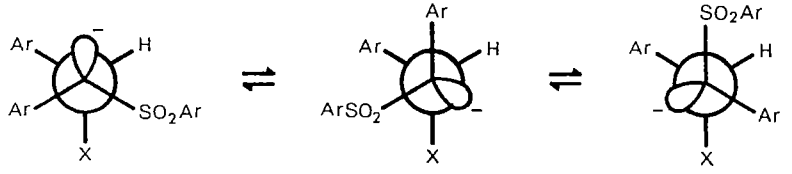
284 286

285 287

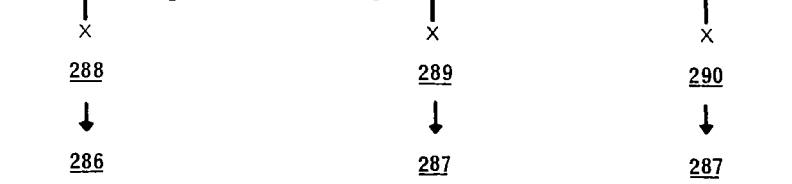
This result has been clearly explained by Bartsch and Závada as quoted from their recent review on the olefin-forming E2 and ElcB eliminations (83).

> "Proton abstraction from the erythro substrate 284 leads to a mixture of rapidly equilibrating pyramidal carbanions 288-290. However, the elimination proceeds only via carbanion 288 because its electron pair is ideally situated for expulsion of the leaving group and at the same time, Ar-$ArSO_2$ steric interactions are minimized in carbanion 288. Therefore a clean anti elimination takes place."

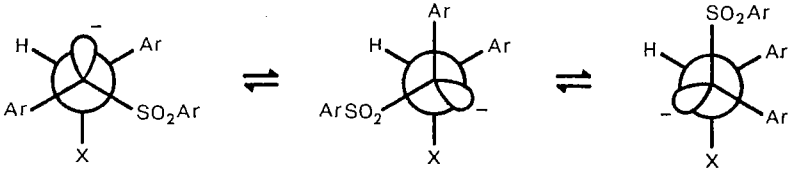
> "In elimination from the threo compound 285, the situation is different because the stereoelectronic and conformational factors are not cooperative. Since expulsion of the leaving group from the stereoelectronically preferred carbanion 291 is rendered difficult by severe Ar-$ArSO_2$ steric interactions, the anti elimination is slowed down and syn elimination via carbanions 292 and 293 become competitive."



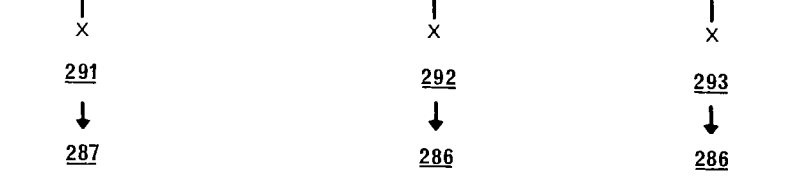
288 ⇌ 289 ⇌ 290



286 287 287



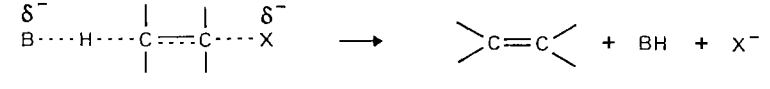
291 ⇌ 292 ⇌ 293



287 286 286

The same authors have further pointed out that the syn elimination from 292 and 293 might require a configurational inversion of the carbanion, so that the electron pair becomes antiperiplanar to the leaving group.

In the concerted mechanism (E2), both the C—H and the C—X bonds are cleaved simultaneously via a single transition state (294). The concerted 1,2-elimination depends however upon the dihedral angle θ between the C—H and the C—X bonds, which are going to be broken in the activated complex. Experiments on rigid systems have shown that the activation energy for elimination has two minima corresponding to the antiperiplanar (θ=180°C, cf. 295) and synperiplanar (θ=0°C, cf. 296) arrangements of the departing groups. This is a strong indication that stereoelectronic effects play an important role in this reaction.



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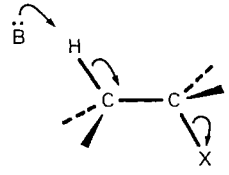

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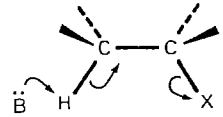
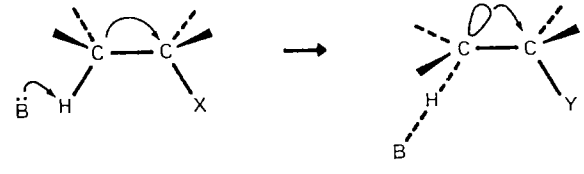


296

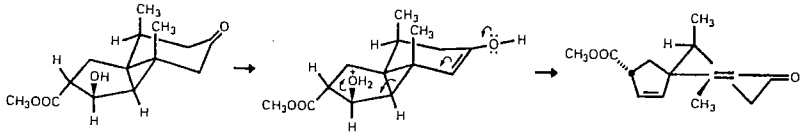
In conformationally mobile systems, both syn and anti eliminations are theoretically possible. The anti elimination should be favored electronically over the syn elimination because the electron pair of the C—H bond is antiperiplanar to the leaving group. It has also been suggested (84, 85) that the syn elimination might require a configurational inversion at the C—H bond, so the electron pair of that bond becomes antiperiplanar to the C—X bond (297 → 298).



297 298

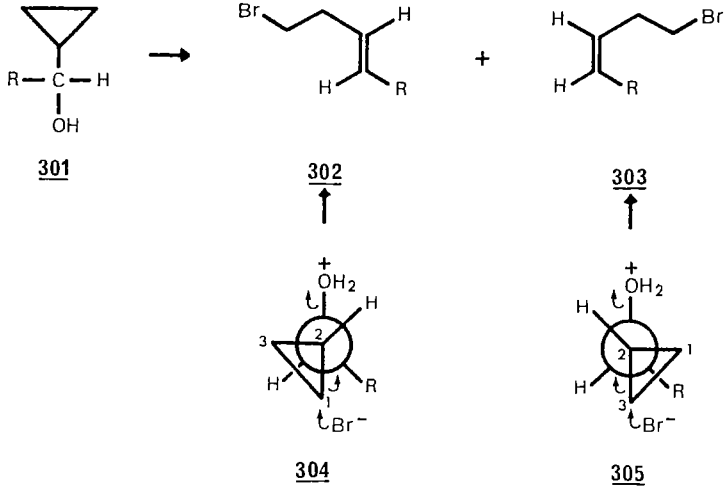
It would appear safe to conclude that where stereoelectronic effects alone are operating, the anti elimination process is favored over the syn. There are however several other parameters which are also important, such as the effects of the nucleophile, the solvent, the alkyl structure of the substrate and the nature of the leaving groups. Any of these variables is capable of completely reversing the stereochemical course of a concerted elimination reaction (83).

The stereochemical implication for the ejection of a leaving group in the β-position of a carbonyl group which yields an α,β-unsaturated system has been treated elsewhere (see p. 233). It may be pointed out here that double bond formation through the opening of a cyclopropane ring should also take place following the same stereoelectronic principle. One example of such a reaction is the transformation of β,γ-cyclopropyl-δ-hydroxyketone 299 which is smoothly converted into the dienone 300 (86) under acid conditions.



299 300

Julia and co-workers (87, 88) have developed a novel synthesis of homoallylic bromides by rearrangement of cyclopropyl carbinols on treatment with hydrobromic acid. For instance, the secondary cyclopropyl carbinols 301 have been converted into trans-bromo olefins 302 with 90-95% stereoselectivity.



301 302 303 304 305

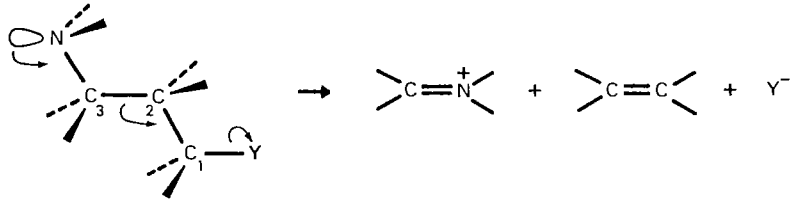
The Newman projections 304 and 305 illustrate the required transition state geometries for a concerted process leading to the trans and cis-bromo olefins 302 and 303 respectively. Models show that severe non-bonded steric interactions between the C_1 and C_3 methylene groups and the R group strongly destabilize arrangement 305 relative to 304 so that the predominant formation of the trans olefin 302 (from 304) is readily explained.

In a modification of Julia's procedure, Johnson and co-workers (89) have shown that the treatment of cyclopropyl bromide (301, OH=Br) with anhydrous zinc bromide in ether gave smoothly the trans-homoallylic bromide 302. Only trace amounts of the cis isomer 303 were formed. This result can be ratio-

nalized by using a combination of the steric and stereoelectronic arguments as discussed above.

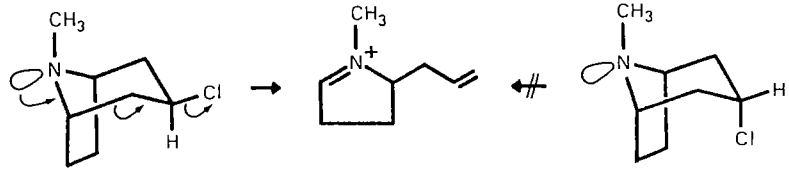
1,4-Elimination

Grob (90) has carried out an extensive study on the fragmentation of γ-amino alcohol derivatives. He has shown that a one-step synchroneous fragmentation takes place only when the compound can adopt conformation 306 where the leaving group is antiperiplanar to the C_2-C_3 bond and the nitrogen electron pair is oriented antiperiplanar to the C_2-C_3 bond. When these γ-amino alcohol derivatives have a stereochemical arrangement other than 306, substitution of the leaving group and elimination reactions take place, but fragmentation is not observed.



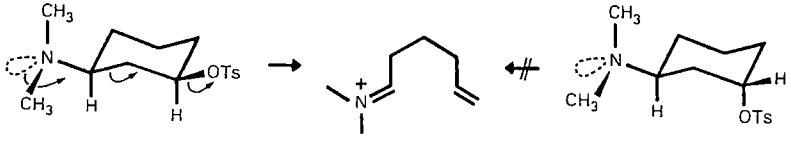
306

For instance, the equatorial chloroisomer 307 gave smoothly the cyclic iminium ion 308. On the other hand, the axial isomer 309 yielded substitution and elimination products but no 308. Also, 307 reacts 13,500 times faster than the carbon analog of 307 (NCH_3 replaced by CH_2).



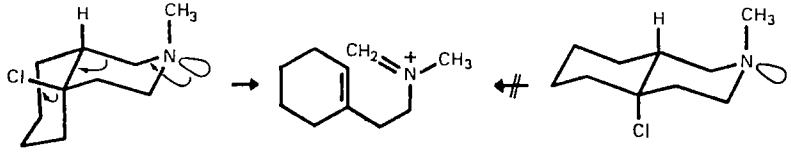
307 308 309

Similarly, compound 310 gave the iminium ion 311 in quantitative yield, while the isomer 312 reacted at a slower rate to give a complex mixture of products. Also, 310 is 35 times more reactive than the carbon analog of 310 ($((CH_3)_2N$ replaced by $(CH_3)_2CH$).



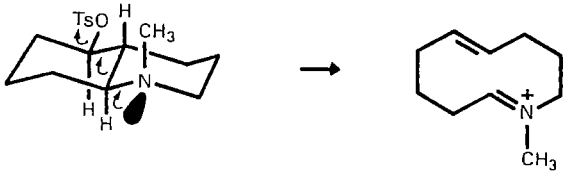
310 311 312

The cis bicyclic chloroamine 313 reacted at a faster rate than the corresponding decalin system 313, (NCH_3 replaced by CH_2) and gave exclusively the cyclohexene iminium salt 314 while the chloroamine 315 reacted to give a mixture of other products.

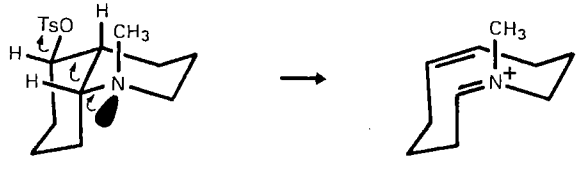


313 314 315

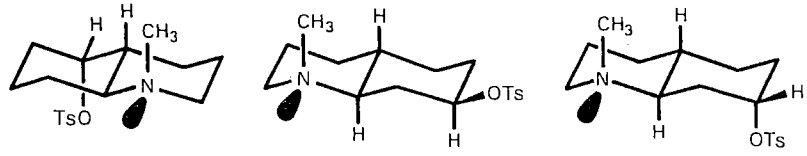
The bicyclic aminotosylates 316 and 317 gave exclusively the trans and the cis iminium salts 318 and 319 respectively. On the other hand, the other three isomers 320, 321, and 322 gave only substitution and elimination reactions.



316 318

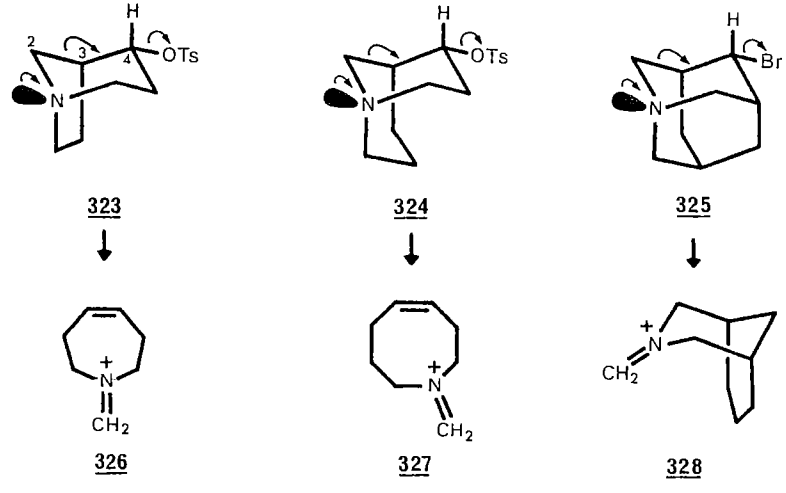


317 319



320 321 322

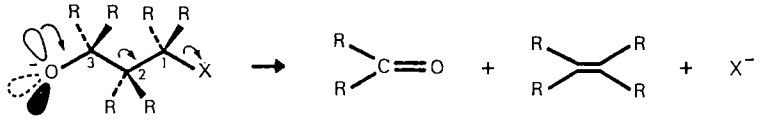
The aminotosylates 323 and 324 and the equatorial 4-bromo-adamantane 325 undergo a quantitative fragmentation to give the iminium salts 326, 327, and 328 respectively (91). Moreover, they react some 10^3, 10^4, and 10^5 times faster than their respective nitrogen-free parent compounds. These azabicyclic systems thus react by a concerted mechanism because the nitrogen electron pair and the C_2-C_3 bond and the leaving group are respectively oriented antiperiplanar. Unexpectedly, fragmentation also took place with the C-4 isomeric products of 323, 324, and 325, but the rates of the reactions were lower.



323 324 325

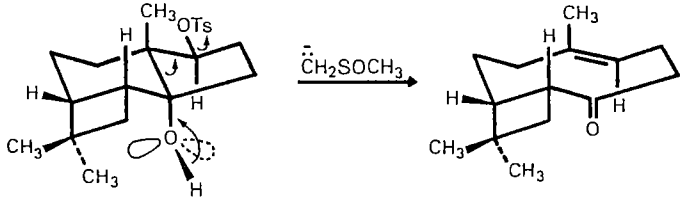
326 327 328

Fragmentation can also occur when the heteroatom is an oxygen atom and again the concerted mechanism is restricted to the molecular geometry 329 where the C_2-C_3 bond is antiperiplanar to the leaving group. There are several examples of this fragmentation in the literature and only a few typical examples will be reported here.



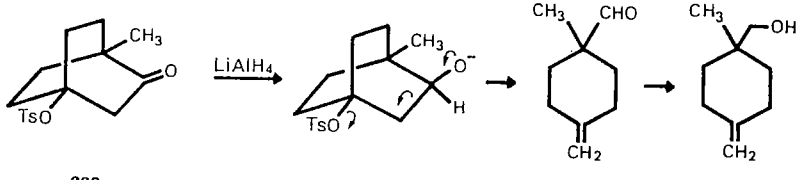
329

Corey, Mitra, and Uda (92) in their synthesis of caryophylene have found that the tricyclic hydroxy-mesylate 330 was converted under basic conditions into the bicyclic ketone 331 having the double-bond with the desired E geometry.



330 331

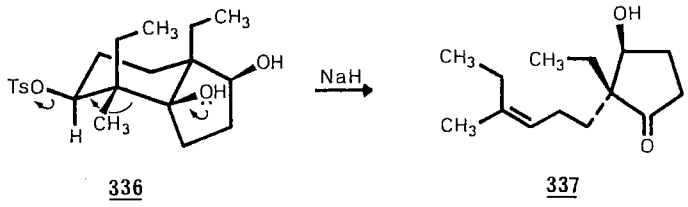
Reduction of the bicyclic ketotosylate 332 which gave the exo-methylene primary alcohol product 335 via the intermediates 333 and 334 was observed by Kraus (93).



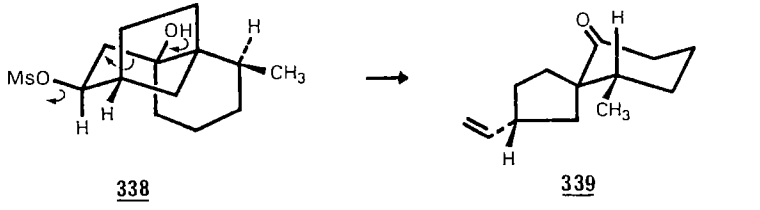
332 333 334 335

Siddall and co-workers (94) in their synthesis of juvenile hormones observed the clean base-catalyzed conversion of 336 into 337 while Marshall and Brady (95) utilized the fragmentation 338 → 339 in their synthesis of hinesol.

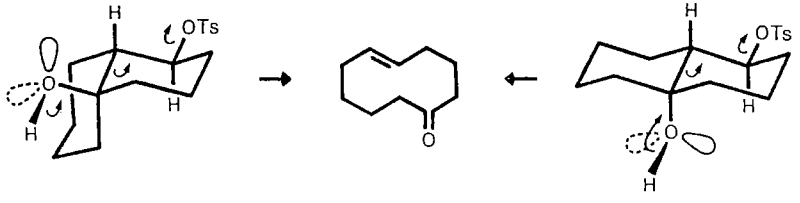
Wharton and Hiegel (96) found that upon treatment under basic conditions, cis and trans hydroxytosylates 340 and 341 yielded the trans olefin 342 while the cis compound 343 gave the cis olefin 344. On the other hand, 345 gave neither 342 nor 344.



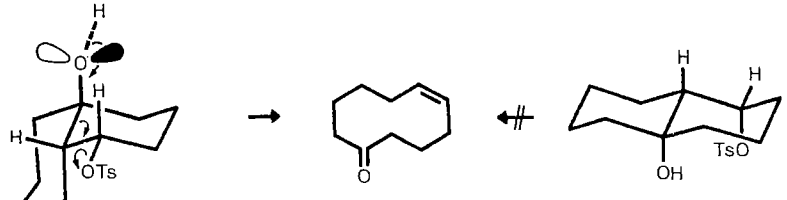
336 337



338 339

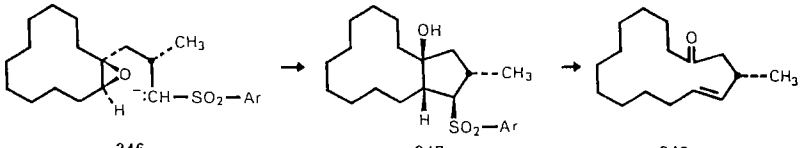


340 342 341



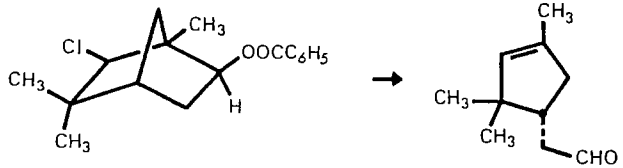
343 344 345

Fischli, Branca, and Daly (97) have reported that epoxysulfone 346 gave stereospecifically the bicyclic alcohol 347 upon treatment with sodium amide in refluxing toluene. Treatment of 347 with potassium t-butoxide gave the enlarged ring ketone 348 (for a similar fragmentation, see ref. 98).

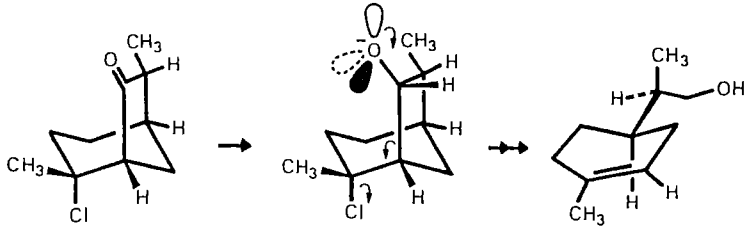


346 347 348

Treatment of the chlorobenzoate 349 with potassium t-butoxide gave the cyclopentane aldehyde 350 (99) while the reduction ($LiAlH_4$) of chloroketone 351 gave the cyclohexene alcohol 353 via the fragmentation of the intermediate 352 (100).

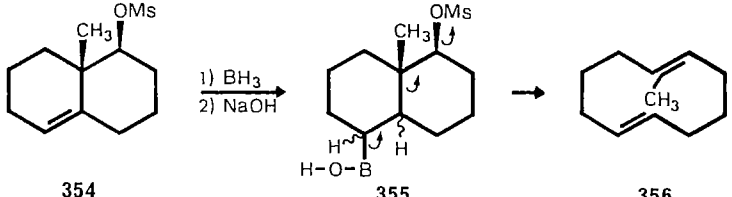


349 350

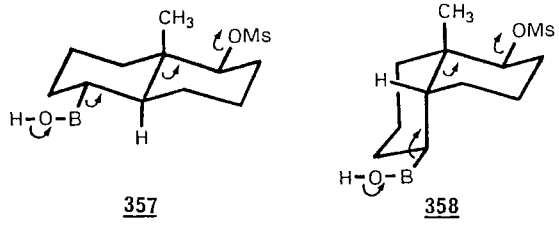


351 352 353

Interestingly, Marshall and Bundy (101) have found that the hydroboration of unsaturated mesylate 354 followed by usual basic treatment gave smoothly the diene 356 via the fragmentation of the intermediate 355. Note that the fragmentation can take place with the two possible stereoisomers 357 and 358.

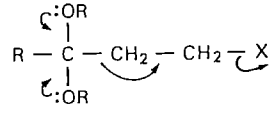


354 355 356



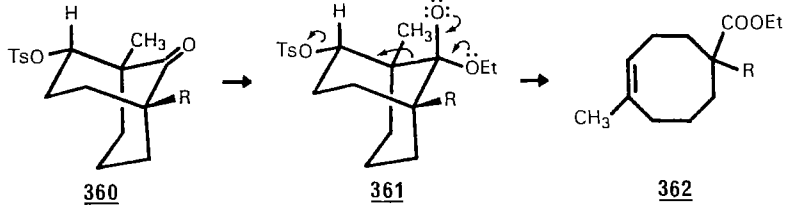
357 358

When two oxygen atoms can participate as in 359, the fragmentation process should occur readily.

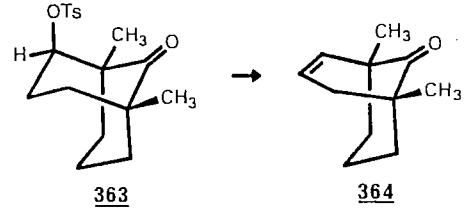


359

It has been reported (102) that the equatorial bicyclic ketotosylate 360 ($R=CH_3$) is transformed into monocyclic olefin ester 362 ($R=CH_3$) by treatment with sodium ethoxide while the axial isomer 363 yielded the bicyclic olefin 364. Similarly, compound 360 ($R=COOCH_3$) gave 362 ($R=COOCH_3$) (103). Thus, reactions with the equatorial tosylates take place via the stereoelectronically controlled fragmentation of intermediate 361 ($R=CH_3$ or $COOC_2H_5$).

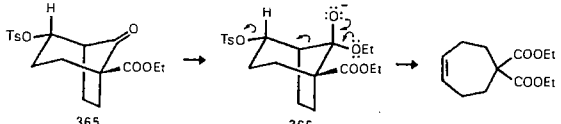


360 361 362

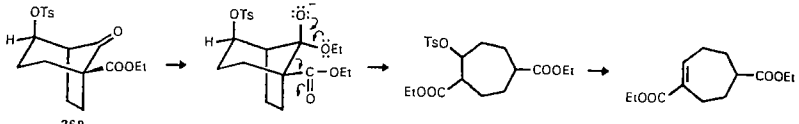


363 364

In another study, Buchanan and McLay (104) found that the equatorial bicyclic ketotosylate 365 gave the seven-membered olefinic ester 367 while the axial isomeric tosylate 368 gave the seven-membered olefinic ester 371. Again, the reaction of the equatorial tosylate occurs through the fragmentation of intermediate 366. The transformation 368 → 371 can be explained by the stereoelectronically controlled retro-Dieckmann fragmentation of 369 followed by the elimination of the tosylate group from 370.

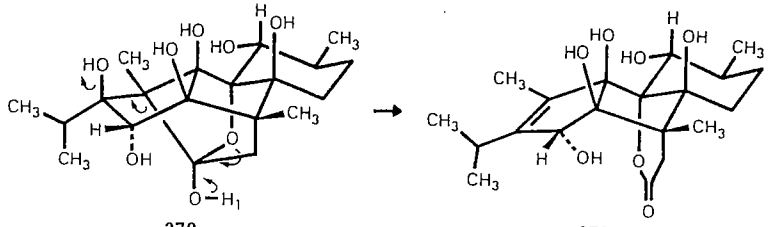


365 366 367



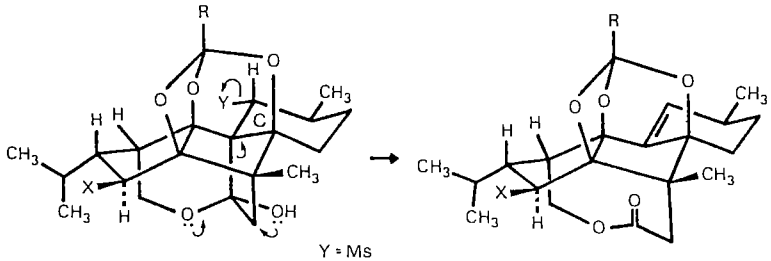
368 369 370 371

The facile acid-catalyzed conversion of ryanodol (372) into anhydroryanodol (373) is another example of this process (105, 106). The fragmentation also occurs under basic conditions (NaH, THF), indicating that when one of two oxygen atoms is negatively charged (372, $O-H_1 = O^-$), the reaction can proceed even if the leaving group is a hydroxyl ion (107).



372 373

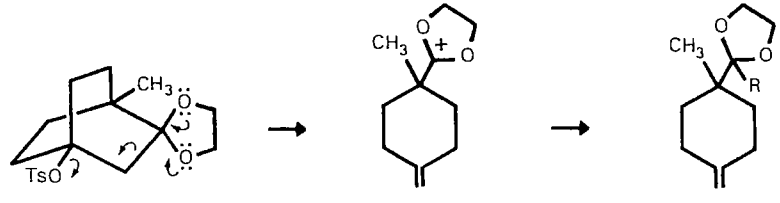
A similar fragmentation was also observed in the course of the total synthesis of ryanodol (108). Intermediate 374 was cleanly transformed into the lactone olefin 375. This fragmentation must however be the result of a syn elimination with ring C of 374 in the boat form.



374 375

Y = Ms
X = $CH(OCH_3)_2$

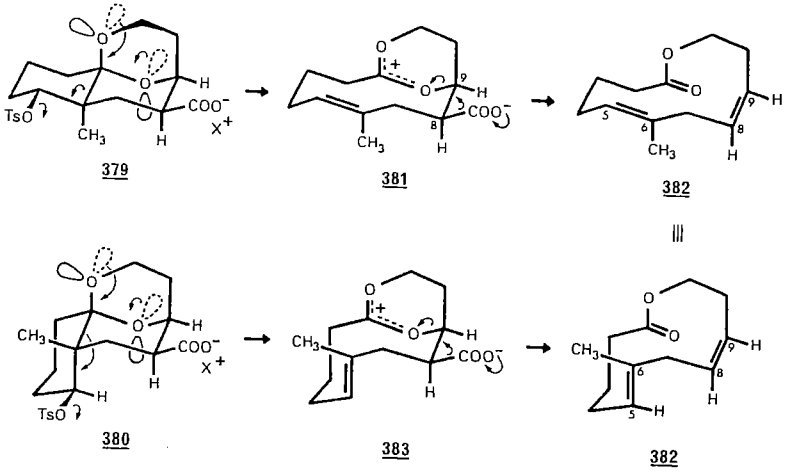
Interestingly, the reduction ($LiAlH_4$), or the Grignard reaction (CH_3MgI), of the ketal tosylate 376 gave ketal 378 (R=H or CH_3) (109). The two oxygens of the ketal function in 376 have each an electron pair oriented antiperiplanar to ease the fragmentation process to give the dioxolenium ion intermediate 377.



376 377 378

Eschenmoser and co-workers (110, 111) have recently carried out a series of decarboxylative double fragmentations which are completely stereoelectronically controlled. This work led to a new synthesis of unsaturated macrolides.

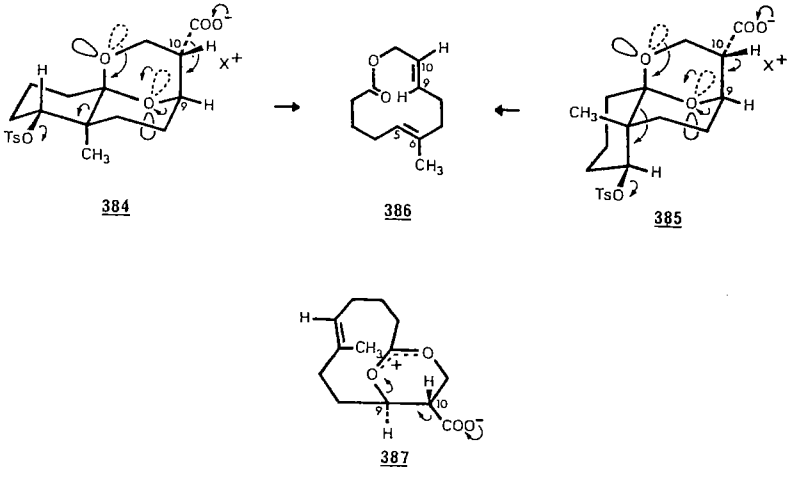
Heating the carboxylic acid salts 379 and 380 (X^+ = amidinium ion) at their melting points (180 and 220°C respectively) gave the 5-E, 8-Z macrolide 382 in high yield. Eschenmoser has pointed out that these fragmentations probably take place in two consecutive steps. In the first step, the two oxygen atoms have each an electron pair properly oriented to eject the tosylate ion via the cleavage of the central C – C bond, producing the dipolar ions (381 and 383). Thence, in the second step, the C_8-C_9 Z double-bond is produced by a stereoelectronically controlled decarboxylation which occurs in an anti mode (C_8-COO^- bond being antiperiplanar to the C_9-O bond).



379 381 382

380 383 382

Confirming the above results, heating the carboxylic acid salts 384 and 385 (X=amidinium ion) for 1 min at their melting points (165° and 195°C respectively) gave a high yield of the 5-E, 9-E isomeric macrolide 386. Note again that, in the dioxolenium intermediate 387, the $C_{10}-COO^-$ bond becomes antiperiplanar to the C_9-O bond and consequently the decarboxylation produces an E double-bond.

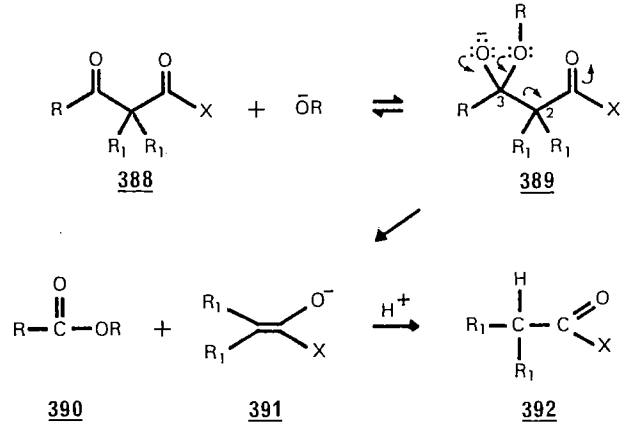


384 386 385

387

Retro-Claisen reaction

The retro-acylation reactions of β-ketoaldehydes (388, X=H), β-diketones (388, X=alkyl) and the retro-Claisen reaction of β-ketoesters (388, X=OR) occur through the formation of an intermediate 389 which gives an ester 390 and the enolate ion 391. Protonation of 391 then gives the corresponding aldehyde (392, X=H), ketone (392, X=alkyl) or ester (392, X=OR).

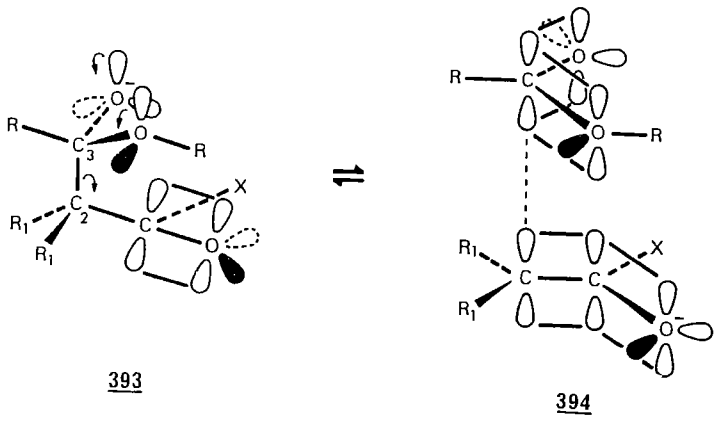


388 389

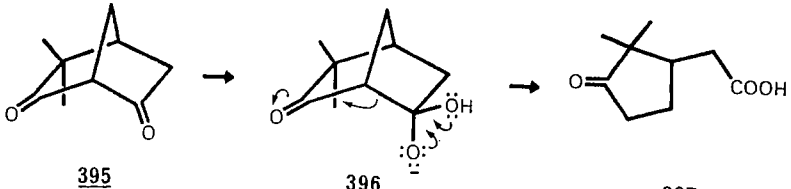
390 391 392

This process can take place with stereoelectronic control only if the two oxygen atoms at C_3 in 389 have each an electron pair oriented antiperiplanar to the C_3-C_2 bond and if this bond is parallel to the π system of the carbonyl group. Thus a conformation such as 393 is required for this reaction. Consequently, in the reverse process 394 → 393, the two reactants should approach each other as shown by 394.

It is well known that bicyclic β-diketones are readily cleaved by hydroxide or alkoxide nucleophiles. For instance, diketone 395 gives readily the keto-acid 397 via intermediate 396 (112). This is a stereoelectronically allowed process.

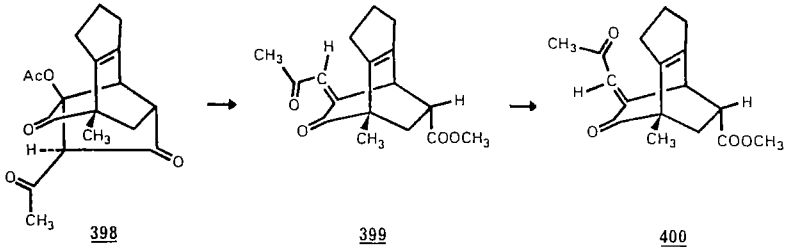


393 394

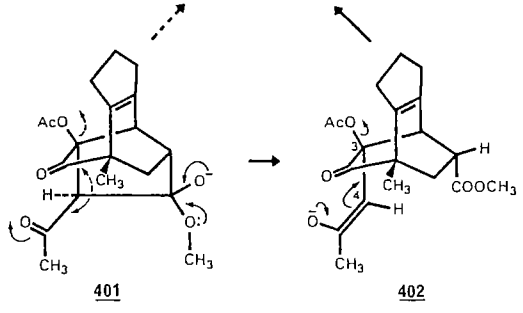


395 396 397

Several examples of retro-Claisen type fragmentations have been observed in the work toward the synthesis of ryanodol. Treatment of triketone acetate 398 with sodium methoxide gave specifically the cis-enedione ester 399. On heating, 399 isomerized to the more stable trans-enedione 400 (113, 114). Methoxide ion reacts with 398 to give intermediate 401 which undergoes a retro-Claisen fragmentation to 402. Loss of acetate ion from 402 yields the cis isomer 399. The last step must be faster than the rotation of the $C_3 - C_4$ bond in 402 as this would have allowed the production of the trans isomer 400 directly from 402. It is also possible that the formation of the cis isomer is the result of the direct fragmentation (Grob type) of 401 into 399 (dotted arrow).



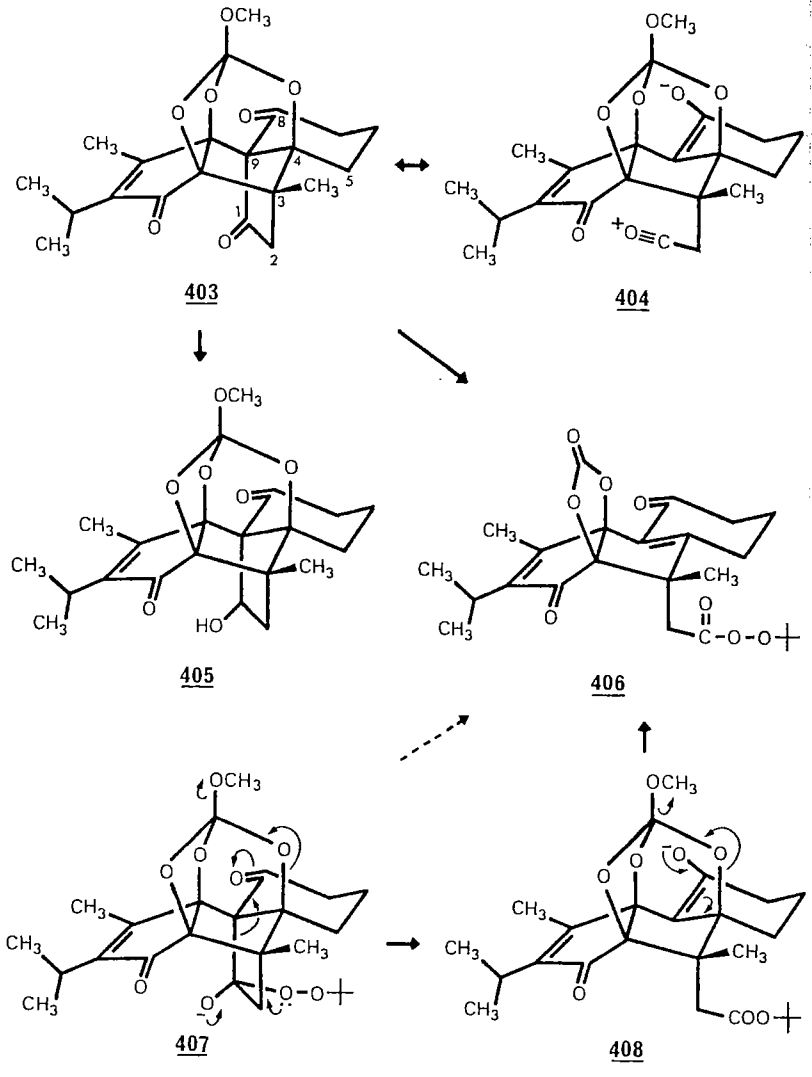
398 399 400



401 402

The reactivity of triketone orthocarbonate 403 is very interesting. The most hindered carbonyl group, i.e. $C_1 = O$, is the most reactive one towards nucleophilic addition. This behavior can be rationalized by the fact that the $C_1 - C_9$ bond is parallel to the π system of the carbonyl group at C-8. Indeed, this compound can be viewed as the hybrid of resonance structures 403 ↔ 404.

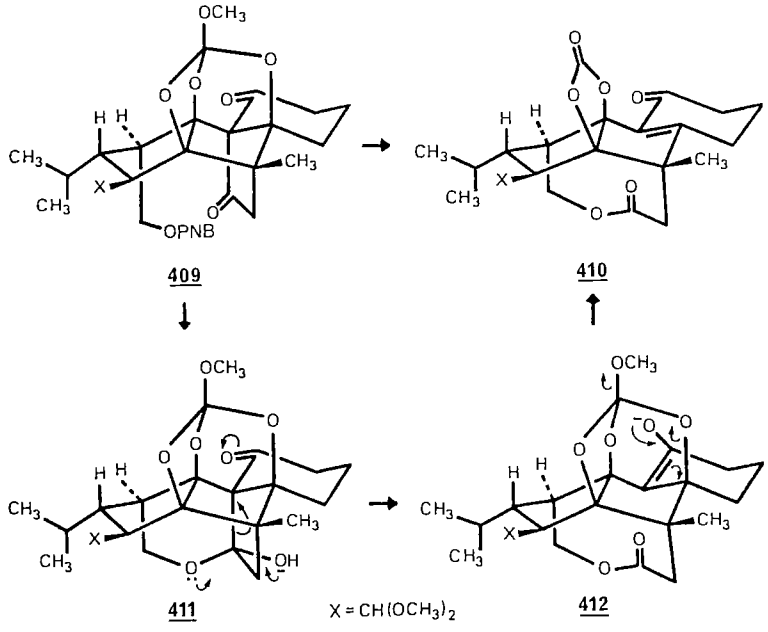
Compound 403 is readily reduced with sodium borohydride at -78°C and yields the monoalcohol 405 (115). It also reacts with potassium t-butyl hydroperoxide at -20°C and gives the cis-enone-perester carbonate 406 in high yield (116). This last transformation can be explained by retro-Claisen fragmentation of intermediate 407 followed by the elimination of methoxide ion from 408. It is also possible that 407 undergoes a direct stereoelectronically controlled Grob type fragmentation to compound 406.



403 404 405 406 407 408

In another study (117), hydride reduction ($LiBH(sec\text{-}Bu)_3$) of the p-nitrobenzoate diketone 409 gave the carbonate enone lactone 410 in high yield. Reduction of p-nitrobenzoate ester must have produced the hemi-ketal inter-

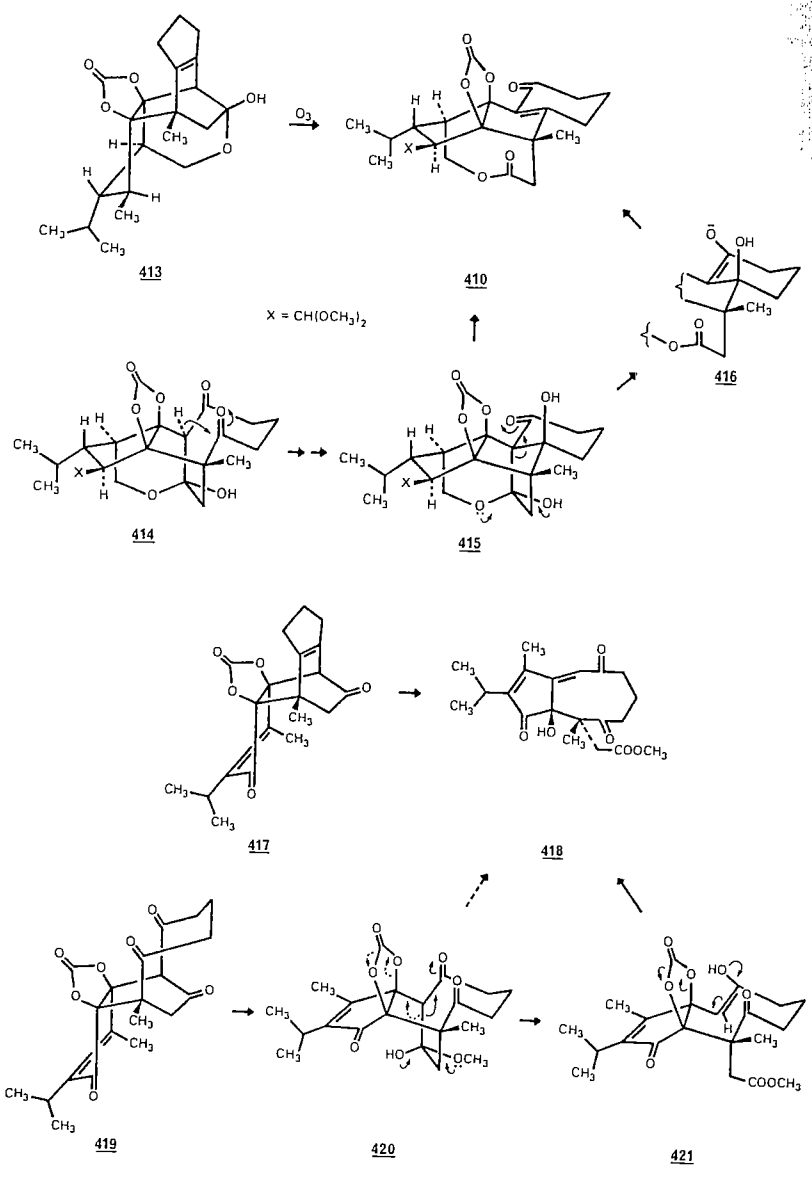
mediate 411 which underwent an internal retro-Dieckmann fragmentation to 412 which could then lose methoxide ion to form compound 410.



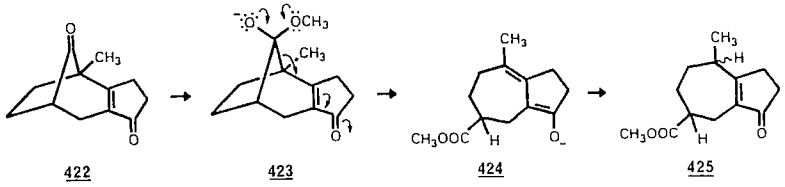
409 410 411 412 X = $CH(OCH_3)_2$

The enone lactone 410 could also be obtained in a single operation from the ozonolysis in methanol of hemi-ketal 413 (118). In this reaction, 413 produced first the diketone 414 which underwent an internal aldol condensation to 415 which is nicely set up to give 410 via the intermediate 416.

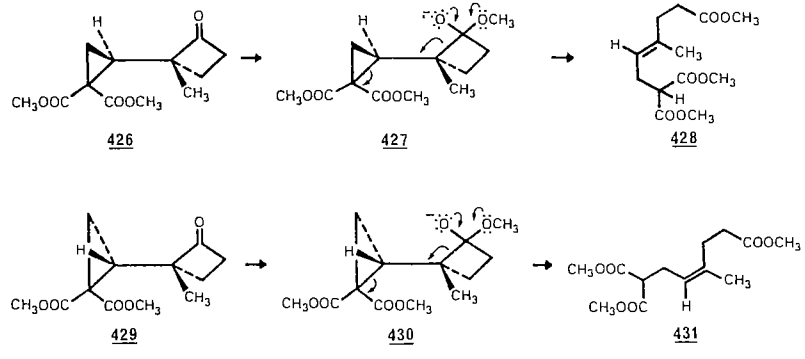
Ozonolysis of diketone carbonate 417 in methanol afforded an almost quantitative yield of the bicyclic diene triketone hydroxy-ester 418 (119). This remarkable transformation can also be readily explained. Ozonolysis of 417 produces the tetraketone intermediate 419 followed by methanol addition to produce the hemi-ketal 420 which undergoes a retro-Claisen reaction to 421. Then, loss of carbon dioxide from 421 yields 418. Again, 420 could also undergo a Grob type fragmentation to yield 418 directly.

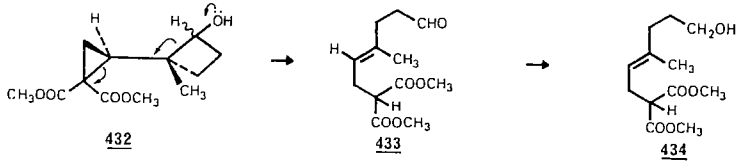


Buchanan and Young (120) have reported the methoxide-catalyzed conversion of tricyclic enedione 422 into a mixture of isomeric esters 425. This reaction can also be explained by the stereoelectronically allowed fragmentation 423 → 424.



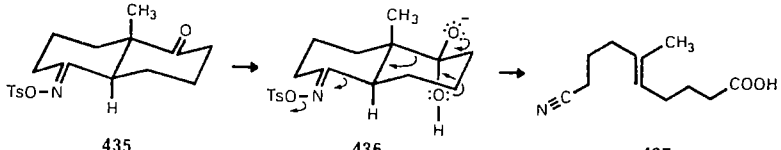
Trost and Frazee (121) have reported a very interesting stereospecific Grob type fragmentation where a cyclopropane and a cyclobutane ring are opened simultaneously. Treatment of 426 with sodium methoxide in refluxing methanol gave the E isomer 428 while the same reaction on 429 gave the Z isomer 431 stereospecifically. These fragmentations occur through the stereoelectronically allowed fragmentation of the intermediates 427 and 430 respectively. The same authors have also observed that treatment of keto-diester 426 (OCH_3 replaced by $OC(CH_3)_3$) with a methanolic solution of sodium borohydride in the presence of magnesium methoxide at 0°C and then reflux (to ensure complete transesterification) gave 434. This reaction can be visualized as 426 → 432 → 433 → 434 where the key step is equivalent to a 1,4-elimination reaction.





432 433 434

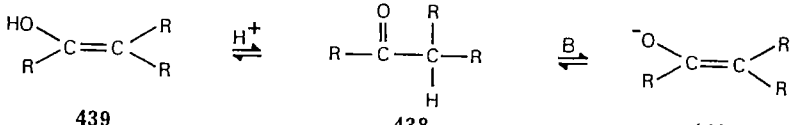
Eisele, Grob, Renk and Tschammer (122) have reported the quantitative transformation of the bicyclic ketone oximetosylate 435 into the cyanocarboxylic acid 437. This reaction occurs through the intermediate 436 and it is interesting to note that the formation of the nitrile function occurs through an anti elimination process.



435 436 437

Enolate ion and related functions

The enolization process, i.e. conversion of a carbonyl compound such as 438 into the intermediate enol 439 or enolate anion 440 is an important reaction in organic chemistry because these intermediates can further react with electrophiles to undergo either protonation, halogenation, alkylation, aldolization, or acylation type reactions.



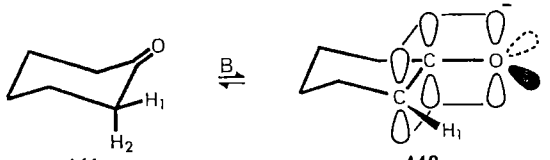
439 438 440

As early as 1953, Corey (123) observed that the kinetically controlled bromination of ketosteroids always gives the epimer in which bromide is "polar" (i.e. axial) and in 1954 (124), he proposed that these results can be explained on the following theoretical basis:

> "Ketonization of an enol and the reverse reaction, enolization of a ketone proceed through the same transition state and hence the same geometrical requirements for minimizing the energy of the transition state hold for both reactions. The energy of the transition state for enolization will be at a minimum when there is

> maximum opportunity for bond formation between the $sp^3 \rightarrow$ p-orbital made available by the leaving hydrogen and the p-orbital of the carbonyl carbon."

> "In the case of a cyclohexanone this implies that in enolization a "polar" (i.e. axial) α-hydrogen is lost in preference to an equatorial α-hydrogen (cf. 441 ⇌ 442). Furthermore, it follows that in the ketonization of an enolized cyclohexanone (e.g. by bromination or protonation) the incoming substituent should adopt preferentially the polar (axial) orientation."

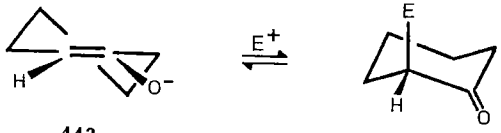


441 442

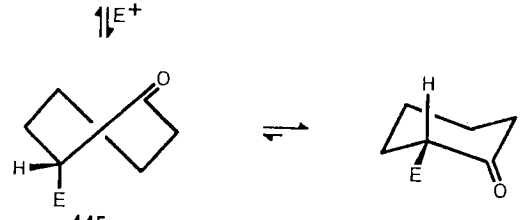
In a subsequent publication, Corey and Sneen (125) mentioned that this "non-steric effect is stereochemical-electronic in nature" and on that basis introduced the term "stereoelectronic". This work (123-125) must therefore be considered one of the very first experimental and theoretical contributions to the principle of stereoelectronic control in organic chemistry.

Subsequently, certain authors (126-128) have supported this interpretation, but alternative explanations have also been proposed (129-132). Another early discussion of the stereochemistry of the enolization process was that of Valls and Toromanoff (133). They proposed that if stereoelectronic effects are an important parameter, the cyclohexanone enolate should react by two different pathways, one involving a chair-like transition state (443 → 444) and the other a boat-like transition state (443 → 445 → 446). Thus, both of these reactions proceed by perpendicular attack (134) of the electrophile. Their energy difference results from the difference in strain between the chair (444) and the twist-boat (445) forms.

The strongest evidence against stereoelectronic control has been the lack of selectivity in the base-catalyzed H — D exchange of 4-tert-butylcyclohexanone, the axial-equatorial rate ratio for exchange being between 5:1 (128) and 3.5:1 (132). However, the low ratio does not hold up as a strong argument, since this ketone can take a twist-boat conformation. Fraser and Champagne (135) have observed a much greater selectivity in the exchange of the conformationally fixed substrate 447, a bridged biaryl ketone. The three-dimensional representation 448 of the bridged biaryl ketone 447 shows that

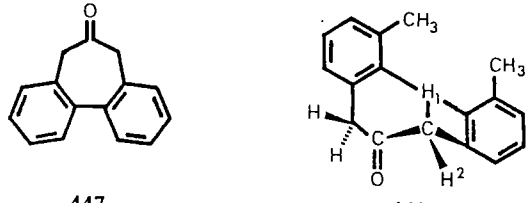


443 444



445 446

the $C-H_1$ bond is parallel to the p-orbital of the carbonyl group and the H_1/H_2 ratio of exchange was found to be 73 using sodium methoxide and 30 using sodium phenoxide in agreement with the principle of stereoelectronic control.



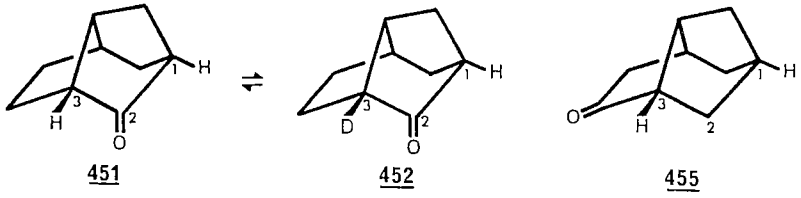
447 448

Stronger support was obtained also by Fraser and Champagne (136), who studied the base-catalyzed $H-D$ exchange reaction of 4-twistanone (449). A Dreiding model of 449 shows that the CH_2-CO fragment is oriented so that one $C-H$ bond alignment (H_1) gives maximum overlap with the adjacent π orbital of the carbonyl function whereas the other $C-H$ bond (H_2) is at a 30° angle to the plane of the π system (cf. the perspective formula 450). Accordingly, when a sample of 4-twistanone was treated with sodium methoxide in methanol-O-d, the relative rates of exchange of the diastereotopic protons H_1 and H_2 were found to be in the ratio 290:1. When a weaker base was used (C_6H_5ONa), this ratio was essentially the same (280:1). The only reasonable explanation for this large difference in the rate of exchange is the effect of stereoelectronic control.

449 450

Interestingly, Wolfe, Schlegel, Csizmadia, and Bernardi (137) have predicted on the basis of ab initio MO calculations, that the enolate derived from the removal of H_1 should be more stable than that from H_2 by 18 kcal/mol when the geometry of the CH_2-CO fragment is similar to that in 450.

Nickon and co-workers (138) have observed that brendan-2-one undergoes a remarkably easy bridgehead exchange at C-3 (451 → 452) under mild basic conditions (CH_3ONa, CH_3OD, 25°C). By comparison, using similar conditions, noradamantan-2-one (453) does not undergo C_3 exchange while bicyclo[3.2.1]-octan-2-one (454) exchanges only its two enolizable protons at C-3.



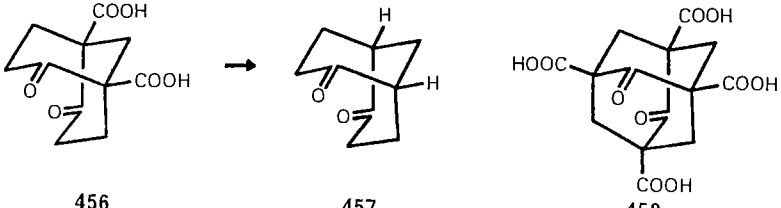
451 452 455

453 454

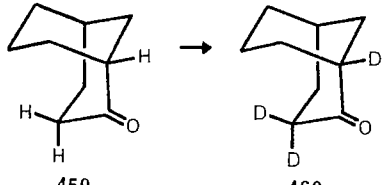
The cyclohexanone ring is locked in a boat form in 451, in a chair form in 453 while it is flexible in 454. As a result, the bridgehead C_3-H bond in 451 is appropriately aligned to overlap with the π orbital of the carbonyl group, whereas it is not in 453 and 454. On that basis, the facile bridgehead enolization of 451 by comparison with 453 and 454 is readily explained by the principle of stereoelectronic control. This is also supported by the

fact that 455 which is isomeric with 451 does not undergo exchange at the bridgehead position. Molecular models clearly indicate that the bridgehead C_3-H bond in 455 is almost perpendicular to the π orbital of the carbonyl group. Consequently, no overlap is possible. These findings support the idea that prior to enolization of equatorial hydrogens, simple cyclohexanones must change from a chair to a boat-like conformation in order to improve initial stereoelectronic alignment as first suggested by Valls and Toromanoff (133) (cf. 446 → 445 → 443).

Meerwein and Schürmann (139) found that the diketodiacid 456 was decarboxylated rapidly (→ 457) in water under relatively mild conditions (≈180°C) for a compound of this structure, while Bootger (140) found that 458 is stable toward decarboxylation. These results together with the base-catalyzed deuterium exchange at the bridgehead position in bicyclo[3.3.1]nonan-2-one (459 → 460) led Schaeffer and Lark (141) to propose the following: the successful decarboxylation of 456 and the facile hydrogen exchange at the bridgehead in 459 are both due to the mobility of the cyclohexanone ring which can adopt a boat form in these compounds. In 458, all rings are locked in the chair conformation and the decarboxylation is thus not favored stereoelectronically.

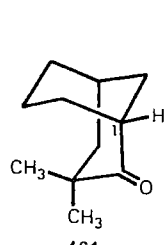


456 457 458



459 460

A more recent investigation by Yamada and collaborators (142) confirms the above results and conclusion. They have studied the base-catalyzed hydrogen-deuterium exchange at the bridgehead position of the bicyclo[3.3.1]nonan-2-one system using the five compounds 460-464. The result on the deuteration of ketone 461 was virtually the same as that of the ketone 460, i.e. ≈45% deuteration of the bridgehead position C-1. There was no significant incorporation of deuterium (≈ 3%) in ketone 462 under the same conditions whereas no deuterium was incorporated into the bridgehead of the ketone 463 which has the gem-dimethyl group at C-3. In contrast, the ketone 464 was found to be easily and exclusively monodeuterated at position C-1 (95% deuterium incorporation).



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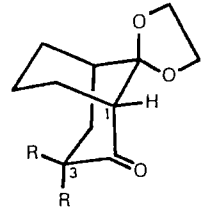
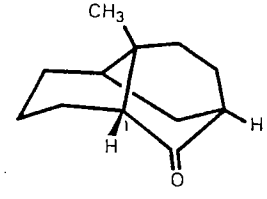


462 R = H
463 R = CH_3



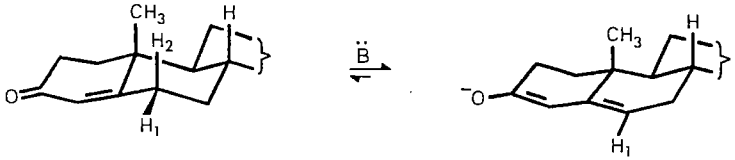
464

Deuterium atom was neatly incorporated at the bridgehead position C-1 in ketone 464, the only compound in which the cyclohexane ring is locked in a boat conformation. Examination of molecular models indicates that the cyclohexanone ring can easily adopt a boat form in 460 and 461. It appears to be more difficult with ketone 462 and almost impossible with ketone 463.

These results strongly support the fact that the enolization of a cyclohexanone via the loss of an equatorial hydrogen must occur through a boat (or a twist-boat) conformation, a consequence of the principle of stereoelectronic control.

Using Δ^4-3-ketosteroids 465, Ringold and collaborators (143) have found that the rate ratio for axial and equatorial proton loss at C-6 is 53. The profound preference for axial proton loss (465 → 466) despite greater steric hindrance from the β face (due to C-19 methyl group) strikingly emphasizes the importance of stereoelectronic effects. In view of this preference, these authors have essentially concluded that cases of equatorial deprotona-

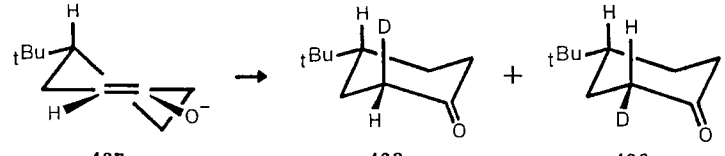
tion must be considered in terms of axial (perpendicular) deprotonation via a non-chair conformation of ring B.



465 466

In principle, reaction of enolate ions with electrophiles should be influenced by stereoelectronic effects. For instance, protonation of enolate ions in acidic medium could provide information about the stereochemistry of the forming of a C—H bond.

House, Tefertiller, and Olmstead (127) have found that the treatment of the enolate ion 467 derived from 4-t-butylcyclohexanone with deuterium oxide in deuterioacetic acid yielded a 7:3 mixture of the axial deuterioketone 468 and the equatorial deuterioketone 469.

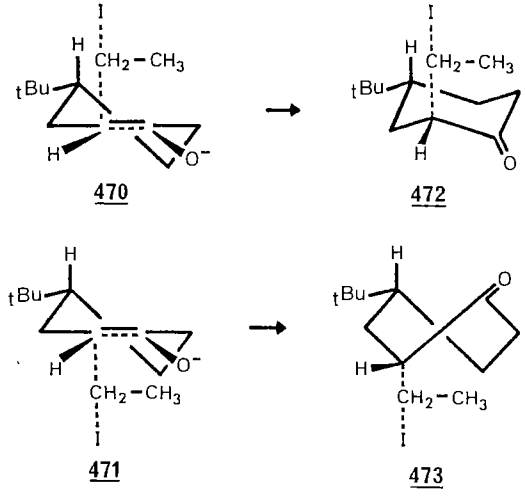


467 468 469

Axial protonation is not strongly favored. They concluded that in practice this type of experiment is complicated by the fact that protonation of an enolate anion can occur either at the carbon (to give 468 or 469) or at the oxygen atom (to yield the enol). Further reaction of the enol with aqueous acid also yields the two possible ketones 468 and 469. Furthermore, since the protonation steps of this strongly basic anion (either at C or O) are diffusion-controlled (144), it is possible that the transition state geometries for both reactions resemble the geometry of the enolate anion, so the energy difference between the direction of attack on the enolate is small.

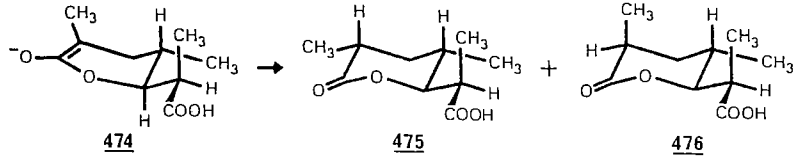
The same authors studied the stereochemistry of alkylation of 4-t-butylcyclohexanone. Alkylation of enolate ion 467 with triethyloxonium fluoroborate yielded a mixture of O-alkyl product and approximately equal amounts of

the stereoisomeric 2-ethyl-4-t-butylcyclohexanones (468 and 469, D replaced by C_2H_5). A comparable mixture of C-alkylated products was obtained using ethyl iodide as electrophile. These results were interpreted as evidence that relatively little new C—C bond formation has occurred at the transition state for the alkylation of enolate anions. For this reason, they proposed that the geometries of the six-membered rings in the transition states resemble much more closely the geometry of the planar enolate anion (e.g. 470 and 471) than the geometry of chair (i.e. 472) or twist-boat (i.e. 473) cyclohexane rings. Huff, Tuller, and Caine (145) have also arrived at a similar conclusion. A more detailed discussion on the stereochemistry of alkylation of enolate ion has been published by House (146).



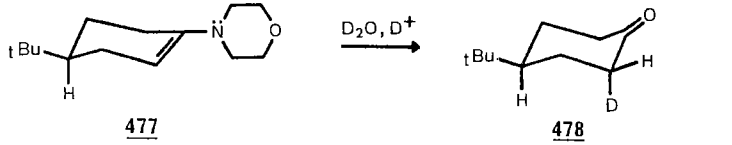
470 472 471 473

Grieco and co-workers (147) have carried out the kinetic protonation at -78° of the lactone enolate 474 and obtained a 3.5:1 ratio of 475 and 476. Axial protonation is again not highly favored. This low selectivity may be due to competing C and O protonation.



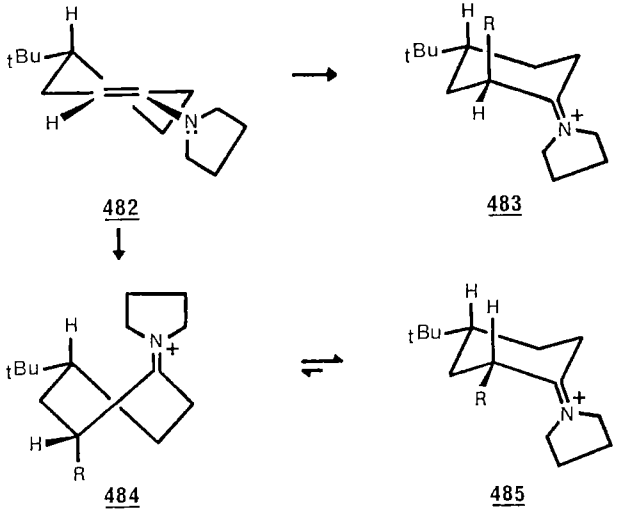
474 475 476

Schaefer and Weinberg have reported (126) that the deuterolysis of 4-t-butyl-1-morpholino cyclohexene (477) produced specifically 2-ß-deuterio-4-t-butyl-cyclohexanone (478). Malhotra and Johnson (148) have shown that the enamine of 2-methylcyclohexanone gives on hydrolysis the cis-deuteromethylcyclo-hexanone 481. This enamine is known to exist in conformation 479 with the methyl group axial. Consequently, axial protonation must have taken place on 479 to give first the iminium ion 480 which was then hydrolyzed to 481.



477 478 479 480 481

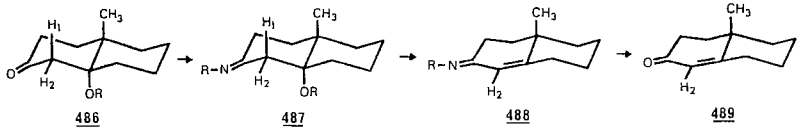
The stereochemistry of the alkylation of enamine 482 has been reported by Karady, Lenfant, and Wolff (149) to give mainly the axial alkylated product



482 483 484 485

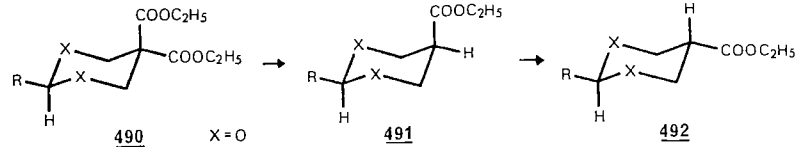
483 [R=CH_3 (70%), $CH_3CH_2CH_2$ (90%), and CH_2 CH−CH_2 (93%)]. The alkylation from the top face (482 → 483) of the enamine is thus preferred over that from the bottom face which would have produced the equatorial iminium ion 485 via the twist-boat 484.

Spencer and co-workers (150) have provided the first evidence for stereo-electronic control in α-deprotonation of iminium ions. Treatment of the ß-hydroxy-ketone 486 (R=H) and the ß-acetoxy-ketone 486 (R=CH_3CO) with weak-ly basic non-tertiary amines ($CF_3CH_2\ddot{N}H_2$ or $\ddot{N}H_2CH_2CN$) gives the bicyclic enone 489 via the formation of imines 487 and 488. Using appropriate deute-rium labeling, they found that the axial proton (H_1) is preferentially re-moved and the stereoelectronic factor was estimated to be 18 (when OR=OH) and 110 (when OR=CH_3COO) in 486. They also found that in the hydroxide ion catalyzed conversion of 486 (R=CH_3CO) into bicyclic enone 489, the axial hydrogen was preferentially abstracted by a factor of 130.



486 487 488 489

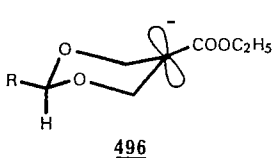
Banks (151) has reported the decarbalkoxylation (NaCl in wet DMSO at 148-153°C) of the geminal diesters 490 and 493. He found that the reaction of 490 was highly stereoselective yielding the axial isomer 491 in preference to the more stable equatorial isomer 492 (ratio ≈9:1). On the other hand, the reaction of 493 was non-stereoselective (ratio ≈1:1 of 494 and 495).



490 493 X=O X=CH_2 491 494 492 495

These reactions likely proceed via the formation of an intermediate carban-ion. Indeed, the carbanion 496 generated by treatment of 491 and 492 with lithium diisopropylamide gave 81% of 491 (H=D) and 19% of 492 (H=D). The preferential formation of 491 can be explained on the basis of stereoelec-tronic effects which influence the reactivity of the intermediate carbanion

496. The sp^2 hybridized carbanion 496 can also be viewed as an sp^3 hybridized anion and can therefore look like 497 or 498. In 497, the electron pair is antiperiplanar to the two C – O bonds of the dioxane ring, so that the carbanion orbital can be delocalized by an overlap with the antibonding orbitals of the two C – O sigma bonds (n-σ* interaction). On that basis, carbanion 496 would be closer to 497 than 498, and the equatorial approach of the electrophile is thus readily understood. Banks has however given a different explanation based on the work of Klein (152, 153).



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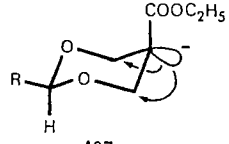

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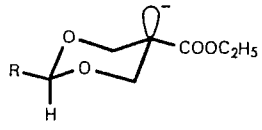
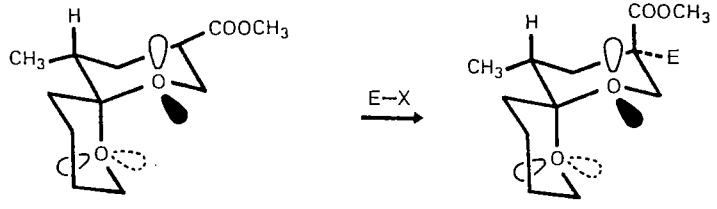


498

Similar experimental results were observed recently in our laboratory (154). Indeed, the lithium enolate of bicyclic spiro ester 499 gave almost exclusively the equatorial product 500 (E= C_6H_5S, CH_3S, C_6H_5Se, CH_3 or I) on reaction with various electrophiles.



499 500

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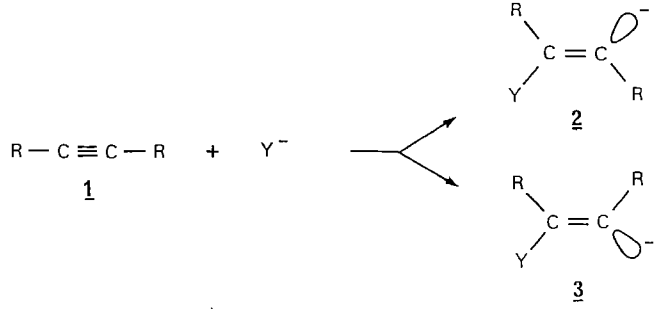
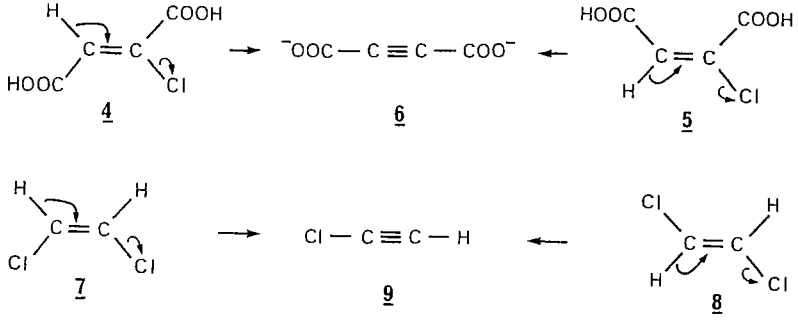
CHAPTER 7

REACTIONS ON TRIPLE-BONDS

The addition of a nucleophile Y to a triple-bond as in 1 can take place to give a product anion where the entering nucleophile is trans (2) or cis (3) to the non-bonded electron pair. Stereoelectronic effects should therefore affect product formation.



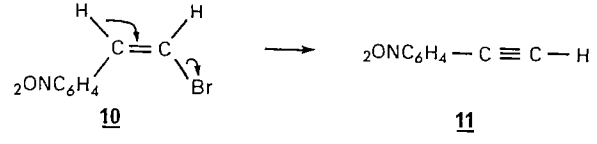
Ingold (1) has mentioned that the older literature contains several observations indicating the existence of stereochemically favorable and unfavorable situations for elimination reactions leading to acetylenic compounds. For instance, Michael (2) found that chlorofumaric acid (4) is converted by alkali about 50 times faster than in chloromaleic acid (5) into acetylene dicarboxylic acid (6). Chovanne (3) has observed that cis-dichloroethylene (7) is transformed by alkali about 20 times faster than is the trans-isomer 8 into chloroacetylene (9).



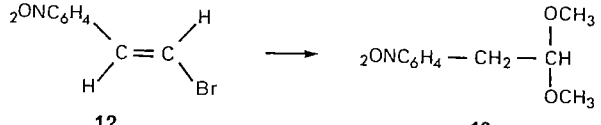
4 6 5

7 9 8

Cristol and co-workers (4) found that cis-p-nitrostyryl bromide 10, in the presence of ethanolic sodium ethoxide, undergoes elimination (yielding 11) 2300 times faster than the trans-isomer 12 which undergoes an alternative reaction of addition (→ 13).

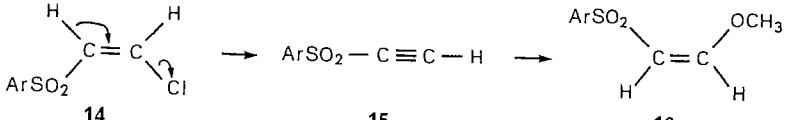


10 11



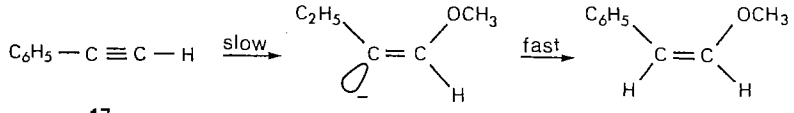
12 13

Modena and co-workers (5) have also reported that cis-β-arenesulfonylvinyl chlorides (14) undergo nucleophilic substitution of the halogen by methoxide ion by way of an E2 trans-elimination to an acetylene derivative (15) followed by a trans-addition to yield the cis-product 16.



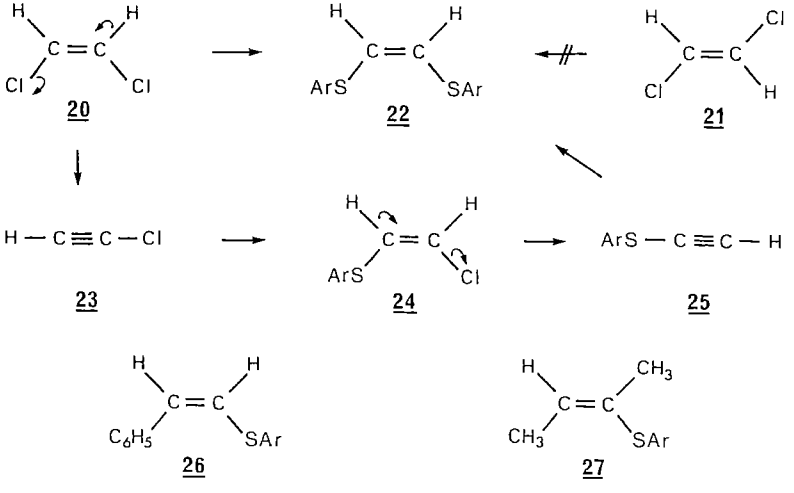
14 15 16

Miller (6) has reported that the methoxide-catalyzed addition of methanol to phenylacetylene (17) gave stereospecifically cis-β-methoxystyrene (19) via the intermediate 18.



17 18 19

Truce and collaborators (7-9) have shown that cis-dichloroethylene 20 reacts readily with sodium p-toluenethiolate in the presence of sodium ethoxide to give cis-1,2-bis-p-tolylmercapto-ethylene 22 while the trans-isomer 21, when subjected to the same conditions is recovered unchanged. Convincing evidence was obtained that the conversion 20 → 22 takes place via the intermediates 23, 24, and 25. Truce and Simms (9) have also observed that the base-catalyzed addition of p-toluenethiol to phenylacetylene and to 2-butyne yields cis-styryl p-tolylsulfide (26) and 2-p-tolylmercapto-trans-2-butene (27) respectively.



20 22 21

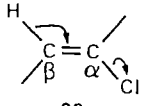
23 24 25

26 27

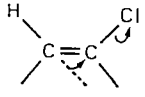
Trans-elimination is therefore clearly stereochemically favored over cis-elimination indicating that stereoelectronic effects must play a decisive role in these reactions. Ingold (1) has pointed out that:

> "... a heterolytic elimination involves an internal S_N2 type substitution at the α-carbon atom, which will be restricted by the exclusion principle to receiving the new electron pair on the side remote from that which the old-electron pair becomes expelled.

Concerted with this process, there is an SE2 type substitution at the β-carbon atom. Such a substitution is not expected to be stereochemically restricted by any adamantine principle. However, the changing electron-pair in substitutions of this type is usually observed to exchange nuclei with retention of configuration of behavior which, in the concerted reaction, leads to trans-elimination, as shown below (cf. 28). If however, in the transition state, the changing electrons were sufficiently released by the departing proton to allow their passage through the β-carbon atom, then their entry by substitution into the β-carbon atom would produce a cis-elimination as illustrated (cf. 29)."

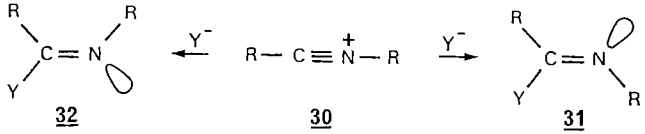


28



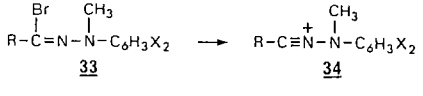
29

More recently, Hegarty has investigated the reactivity of nitrilium ion 30 and found that in the product formed under kinetically controlled conditions, the nitrogen electron pair is always trans to the incoming nucleophile, i.e. 31. In an excellent review (10), Hegarty states that in spite of careful searching, they have unable to observe any detectable quantity of the cis product 32 (or of a product which would be derived from 32 by further chemical transformation).

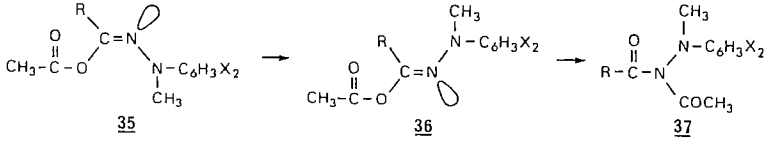


32 30 31

For instance, N-anilinonitrilium ion 34 formed in the solvolysis of hydrazonyl bromides 33 in the presence of sodium acetate at 30°C gives the Z-O-



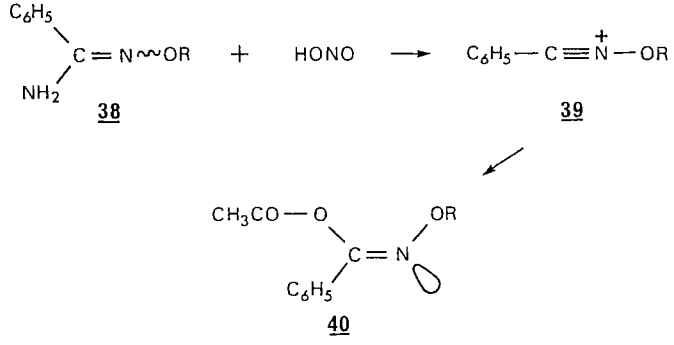
33 34



35 36 37

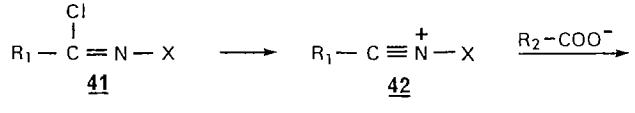
acylisoamide 35 in quantitative yield. On heating, the Z isomer 35 yields the E isomer 36 which is rapidly transformed into the corresponding amide 37 (11).

In another example (12), diazotization of amidoxime 38 gave in situ the nitrilium ion 39 which is trapped by acetate ion as the Z isomer 40.

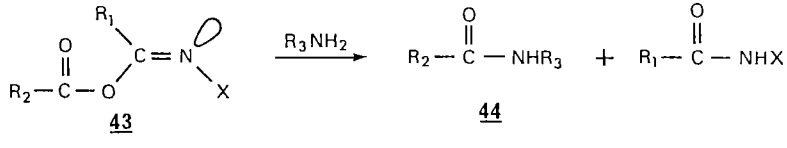


38 39 40

The observation that carboxylate ions react at a much faster rate than amines with nitrilium ions and that they give Z-O-acylisoamides only, has led to the development of a new method for the synthesis of peptides (13). Imide halide 41 on dissolution in a polar solvent undergoes rapid unimolecular ionization to the nitrilium ion 42 which reacts with the carboxylate ion to give the Z-O-acylisoamide 43 which in turn reacts with the amine to give the amide product 44. The formation of the amide (or peptide) can be carried out by adding the halide 41 to a solution containing both the amine and the carboxylic acid. The initial reaction (41 → 42 → 43) is best carried out at pH=6 and when the pH is adjusted to ≈8, formation of the amide (43 → 44)



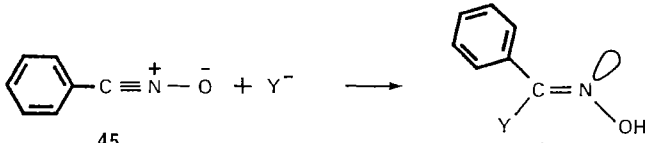
41 42



43 44

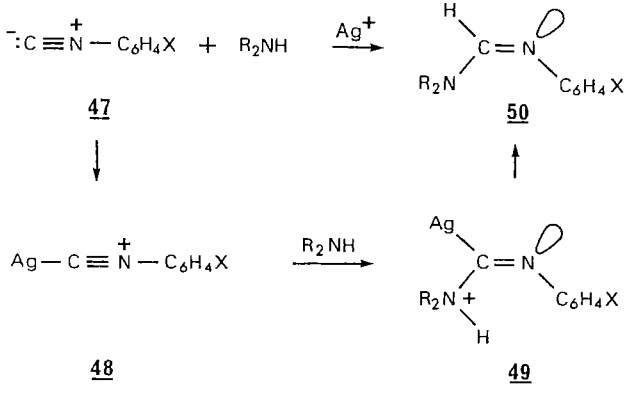
is rapid and complete. A vital feature is that, due to its geometry, the intermediate Z-O-acylisoamide 43 is stable to O→N acyl migration.

Hegarty and collaborators (14-16) have also found that the addition of a large variety of nucleophiles (Y= Cl^-, N_3^-, CH_3O^-, $R-C\equiv C^-$, $R_2\ddot{N}H$, CH_3COO^-, and AlH_4^-) on benzonitrile oxide 45 is completely stereospecific and yields the trans-adduct 46.



45 46

Hegarty and Chandler (17, 18) have found that secondary amines react with isonitriles 47 in the presence of AgCl at low temperature to give the isolable but thermodynamically unstable Z-amidines 50. This reaction is believed to occur via the formation of the metallated nitrilium intermediate 48 which adds the secondary amine stereospecifically to give 49. Compound 49 is then converted into the Z isomer 50.

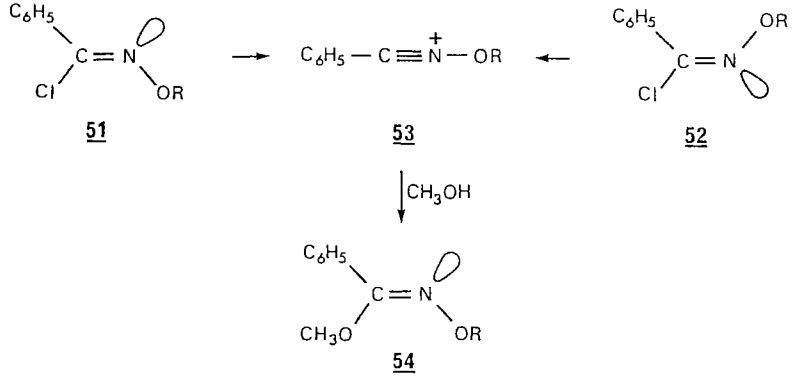


47 50

48 49

The marked stereospecificity observed in the addition of nucleophiles to nitrilium ions should also be apparent in the reverse process, i.e., in the loss of an atom or group leading to the nitrilium ion formation. Johnson and co-workers (19, 20) have prepared several pairs of isomeric O-alkylhydroxamoyl chlorides 51 and 52. These compounds undergo unimolecular loss

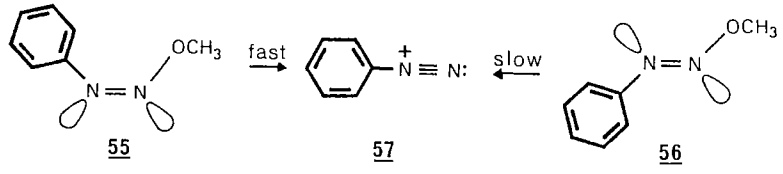
of chloride ion under forcing conditions to give the nitrilium ion 53, and it was found that the Z isomer 51 is far more reactive than the E isomer 52 ($k_Z/k_E \approx 450$). Furthermore, both chlorides yield a single product, the Z isomer 54 on trapping the nitrilium ion 53 with methanol.



51 53 52

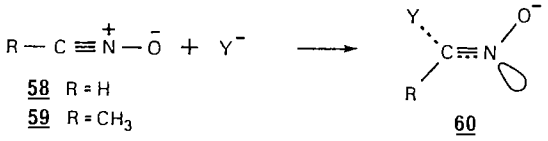
54

Broxton (21) has also observed that the formation of the arenediazonium ion 57 takes place at a much faster rate ($\approx 10^4$) with the Z isomer 55 than the E isomer 56.



55 57 56

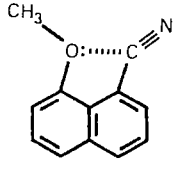
A theoretical study on the addition of nucleophiles to fulminic acid (58) and acetonitrile oxide (59) has been carried out (22, 23). Ab initio calculations show that these compounds are linear in the ground state but are relatively easily deformed. It is markedly easier to bend the atoms in the nitrilium system in a trans fashion rather than in a cis mode. The transition state is reached relatively early when a nucleophile reacts with the nitrile oxide and its configuration corresponds to 60. Thus the configuration of the product is clearly determined at the transition state.



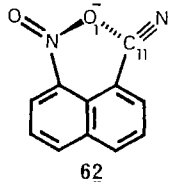
58 R = H
59 R = CH_3

60

Interestingly, the crystal structures of 8-methoxy-1-naphtonitrile and 8-nitro-1-naphtonitrile have been determined by X-ray analysis by Procter, Britton, and Dunitz (24). The structure of the methoxy derivative corresponds to 61 where the exocyclic C − O bond is bent inward (toward the nitrile group), the exocyclic C − CN bond is bent outward (away from the methoxy group). The C − C ≡ N bond angle is 174° instead of 180°. A similar observation has been made with 8-nitro-1-naphtonitrile. Crystals of this compound contain two symmetry independent molecules which differ in structure. Both show a bent C − CN bond and a short O···C ≡ N distance (cf. 62), but the orientation of the nitro group is different with the result that in one molecule the $O_1 \cdots C_{11}$ distance is 2.69 Å whereas in the other, it is 2.79 Å. This analysis is in complete agreement with the theoretical calculations and the experimental results presented above. Thus, it can be concluded that the nucleophilic addition on triple-bond (and the reverse process) is strongly influenced by stereoelectronic effects which favor the anti mode of addition.

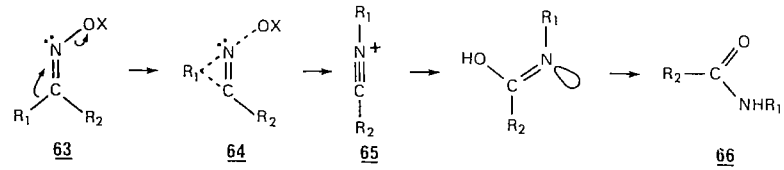


61

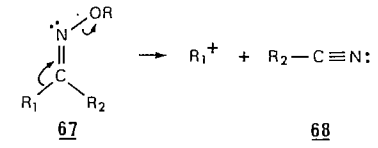


62

The Beckman rearrangement converts oximes (and derivatives) to amides (25-27). In this rearrangement, the group which migrates is the one oriented antiperiplanar to the N − O bond and the stereochemical configuration of the migrating group is retained (cf. 63 → 66). Thus, the R_1 group migrates in preference to the R_2 group forming first the nitrilium ion 65 via 64. Hydration of nitrilium ion 65 followed by tautomerization gives the amide 66. When the potential migrating group can form a relatively stable carbonium ion, fragmentation (67 → 68) takes place instead of migration yielding the corresponding nitrile (see also Chapter 6, p. 274).

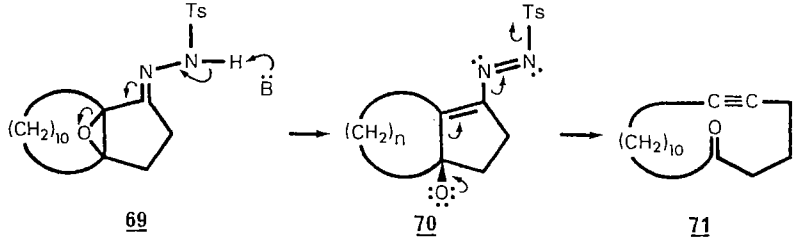


63 **64** **65** **66**

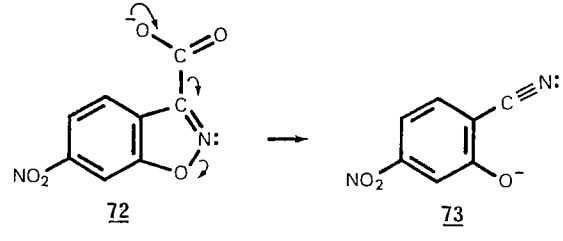


67 **68**

Eschenmoser and collaborators (28) have reported the base induced fragmentation of α,β-epoxy-tosylhydrazones to produce acetylenic ketones (e.g. 69 → 71). Interestingly, in this fragmentation, both the triple-bond and molecular nitrogen are produced from the key intermediate 70 via an anti mode. The decarboxylation of nitrobenzisoxazole carboxylate (72) into 2-cyano-5-nitrophenol (73) can also be viewed as a trans-elimination (29, 30).

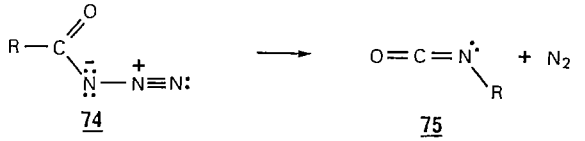


69 **70** **71**

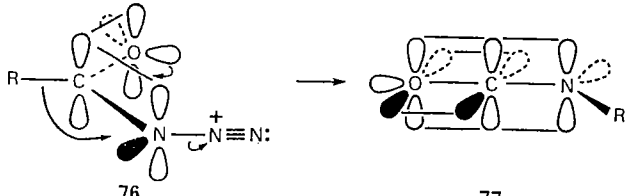


72 **73**

In the Curtius rearrangement of an acylazide which yields as the initial product an isocyanate (74 → 75) and molecular nitrogen, the migrating group retains its stereochemical configuration as in the Beckman rearrangement (26, 27). It is therefore likely that stereoelectronic effects control this rearrangement. The R − C bond must therefore be antiperiplanar to the $N-N_2^+$ bond (76 → 77). Note also that the oxygen atom in 76 has one electron pair oriented antiperiplanar to the migrating R group.



74 75



76 77

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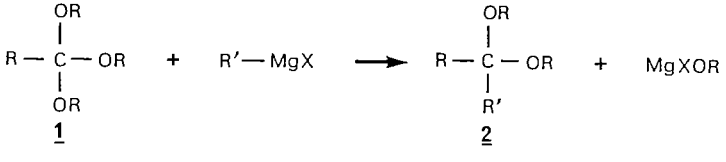
CHAPTER 8

POT-POURRI

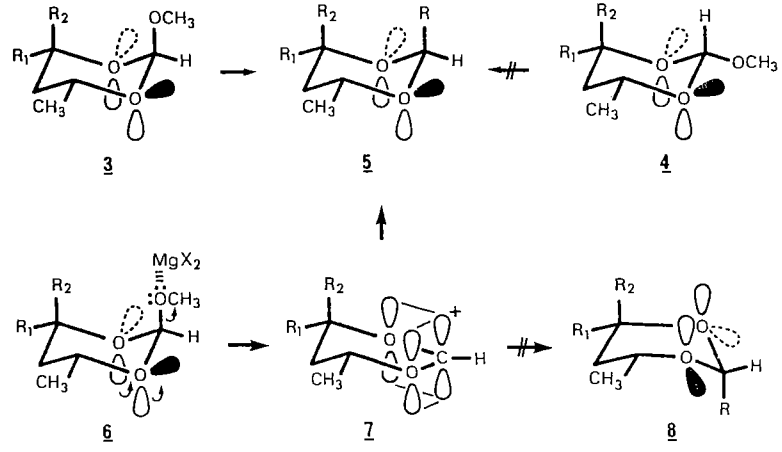
We have seen throughout the previous Chapters of this book that stereoelectronic effects combined with the usual steric interactions strongly influence the conformation and the reactivity of organic molecules. It is also through the understanding of these effects that it becomes possible to consider the stereochemistry of the transition states of many organic reactions. As a result, better synthetic sequences can be elaborated as shown by the several examples described in Chapters 5-7. More examples which cannot be appropriately placed in these Chapters are described here. This Chapter will also show how to use stereoelectronic principles either to imagine and discover organic substances with rather unusual reactivities or simply to develop new strategies in organic synthesis.

Miscellaneous organic transformations

The reaction of orthoesters with Grignard reagents provides a well known route to acetals and ketals (1 → 2). Eliel and Nader (1) have investigated the stereochemistry of this reaction and have concluded that it is governed by powerful stereoelectronic effects.

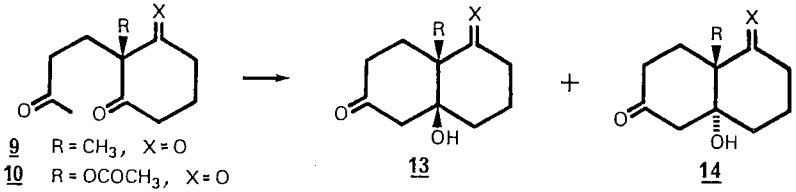


They have studied the reactivity of axial and equatorial 2-alkoxy-1,3-dioxanes 3 and 4 ($R_1=R_2=H$; $R_1=R_2=CH_3$; $R_1=CH_3$ and $R_2=H$). Reaction of axial orthoesters 3 with methyl, ethyl, isopropyl and various p-substituted phenyl Grignard reagents proceeded smoothly at room temperature to give largely the corresponding 2-alkyl-1,3-dioxanes 5 having the 2-alkyl group axially oriented. In contrast, the equatorial orthoesters 4 failed to react under corresponding conditions.



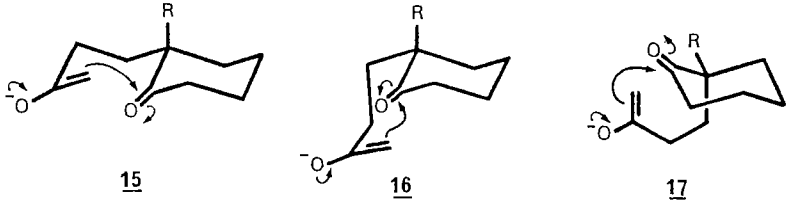
Thus, both the departing alkoxy group and the incoming alkyl group prefer the axial position. In compound 3, the dioxane oxygens have each an electron pair properly aligned to assist the ejection of the leaving group (probably catalyzed by MgX_2 or RMgX, cf. 6) and to form the dioxolenium ion 7. Then, the Grignard reagent attacks the ion 7 from the same side to yield the reaction product 5 having the 2-alkyl group in the axial orientation. Note that the attack of the Grignard reagent on the opposite face of the dioxolenium salt is not favored as it would require a boat-like transition state (7 → 8). Similarly, the low reactivity of the equatorial alkoxy group in 4 is due to the fact that its ejection cannot be stereoelectronically assisted unless compound 4 takes first the unfavorable boat form 8 ($R=OCH_3$). This work and analysis which appeared in 1969-70 (1) is one of the first contributions to the principle of stereoelectronic control in systems derived from the ester function. Bailey and Croteau have recently reported (2) that the products formed from the reaction of 2-methoxy-1,3-dioxane with Grignard reagents depend on reagent substrate complexation and stereoelectronic control.

Spencer and collaborators (3, 4) have observed the cyclization of 9, 10, and 11 under mild basic conditions which yielded the corresponding cis-decalin ketol 13. On the other hand, cyclization of 12 afforded the trans-fused ketol 14 (R=H, X=H_2) exclusively (5). Spencer concluded that the cyclization process must be governed by the size of the incipient angular substituent: when R is small like a hydrogen atom, the transition state leading to the trans-product (cf. 15, R=H) would be of lower energy than that leading to the cis-product (cf. 16 or 17, R=H). However when R is larger than hydrogen, the opposite would be true. So, product formation depends on the steric effect caused by the angular R group and the enolate double-bond. It is however still possible that stereoelectronic effects play also an important role in these reactions. For instance, the approach of the enolate ion to the carbonyl group is different in 15 and 16 than in 17. One approach could therefore be electronically favored over the others, but the experimental results described above give no information on that matter.



9 R = CH_3, X = O
10 R = $OCOCH_3$, X = O
11 R = CH_3, X = H_2
12 R = H, X = H_2

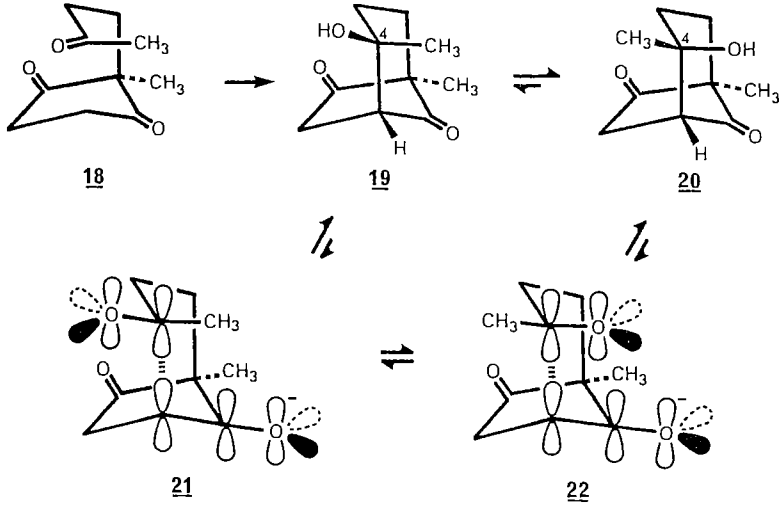
13 14



15 16 17

The first results which indicate that stereoelectronic effects play an important role in the aldol condensation were reported by Hajos and Parrish (6) who found that (a) triketone 18 cyclizes to the bicyclo[3.2.1]octane ketol 19 on treatment with piperidinium acetate in water and (b) ketol 19 undergoes an epimerization at C-4 yielding the more stable isomeric ketol 20 on treatment with piperidine. The authors concluded that the formation of ketol 19 from 18 under kinetically controlled conditions is the result of

"... maximum π-orbital overlap by an almost parallel alignment of the enolic double-bond of the five-membered ring and the carbonyl group in the butanone side-chain."

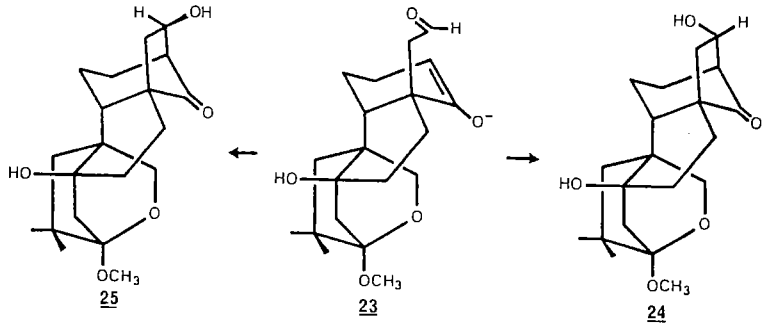


18 19 20

21 22

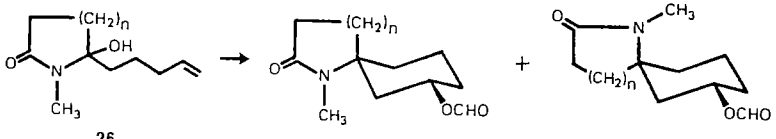
Indeed in the transition state leading to ketol 19 (cf. 21), the enolate double-bond is oriented antiperiplanar to the carbonyl group. This stereochemical approach must therefore be electronically favored over that leading to the isomeric ketol 20. In the last case, the carbonyl group of the side chain is gauche (synclinal) with the enolate double-bond (cf. 22).

In the course of the total synthesis of enmein, Fujita and co-workers (7) have discovered that the intramolecular cyclization of the enolate 23 of the corresponding tetracyclic keto-aldehyde at room temperature gave only ketol 24. However, when the same reaction is conducted at 60°C, thermodynamically controlled conditions prevail, and the epimeric product 25 is obtained. Inspection of molecular models indicates that the kinetically controlled product 24 is again the result of an antiperiplanar arrangement of the enolate and the aldehyde double-bonds. Also, as in the previous examples, the isomer 25 comes from a synclinal arrangement of the reacting functional groups.

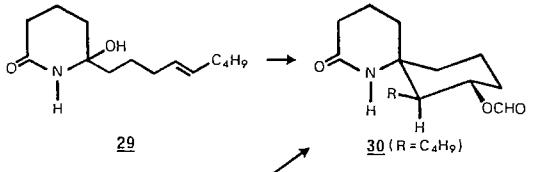


25 23 24

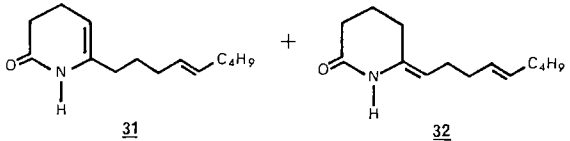
Schoemaker and Speckamp (8) have reported the quantitative conversion of hydroxy-lactam 26 (n=1) (HCOOH, 18 h, r.t.) into the spirocyclic lactam ester 27 (n=1). The other possible spiroisomer 28 (n=1) was not formed. Hydroxy-lactam 26 (n=2) gave spiroisomer 27 (n=2), albeit in lower yield, under similar conditions. The same authors (9) have also reported the successful cyclization of hydroxy-lactam 29 into spirolactam 30. Analogous results were obtained by Evans and Thomas (10) who found that the cyclization of a 9:1 mixture of enamides 31 and 32 in anhydrous formic acid gave the spirocompound 30. This compound is a key intermediate in Kishi's total synthesis of perhydrohistrionicotoxin (11, 12).



26 27 28

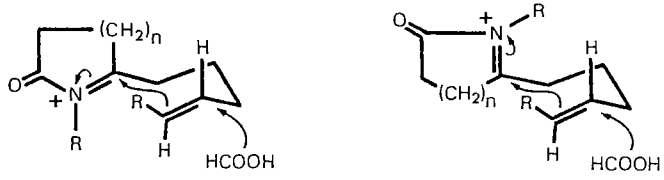


29 30 (R = C_4H_9)



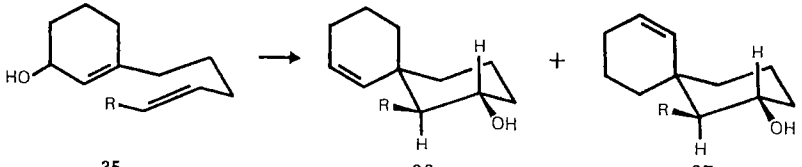
31 32

These results indicate that the cyclization via a chair-like transition state having the iminium cation in a pseudo-equatorial orientation (cf. 33) is more facile than that with an axial orientation (cf. 34). Note again the relative orientation of the iminium cation and the olefinic double-bond which is antiperiplanar in 33 and synclinal in 34.



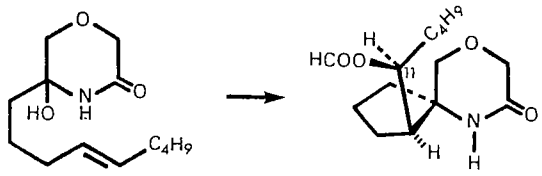
33 34

Antiperiplanarity of double-bonds seems to be an important factor also in carbocyclic cases. Indeed, Harding and collaborators (13) have reported that the intramolecular cyclization of cyclohexenols 35 gave spiroisomer 36 in preference to 37 as the major product (ratio 4:1 when R=H and ≥9:1 when R=CH_3 or n-C_4H_9).

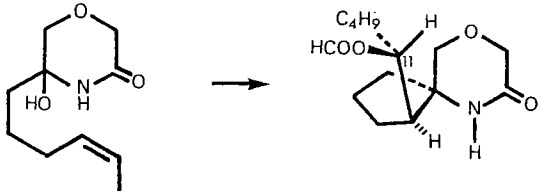


35 36 37

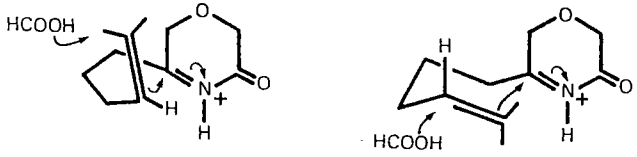
Schoemaker, Kruk, and Speckamp (14) have discovered that the internal cyclization of cyclic α-acyliminium ions with double-bonds takes a completely different course when one methylene group of the ring is replaced by an oxygen atom: treatment of the E-olefin 38 (produced in situ) with formic acid gave the spiro[4.5]bicyclic compound 39 while the Z-olefin 40 yielded the isomeric product 41. The configuration at C_{11} in 39 and 41 depends on the configuration of the starting olefin; their formation can therefore be explained by a synchronous trans-coplanar attack of the α-acyliminium ion and formic acid on the double-bond. An anticlinal (cf. 42) is thus preferred over an antiperiplanar arrangement (cf. 43) in this particular series and it constitutes the first example of a 5-Exo-Trig mode of ring closure which takes place instead of the normally encountered 6-Endo-Trig ring closure.



38 39

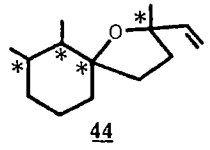


40 41

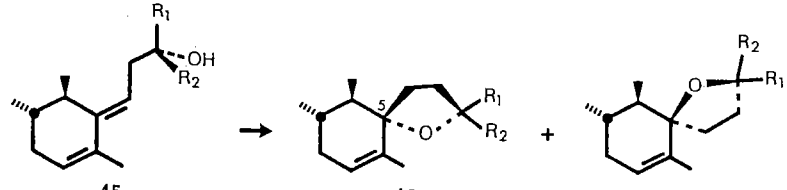


42 43

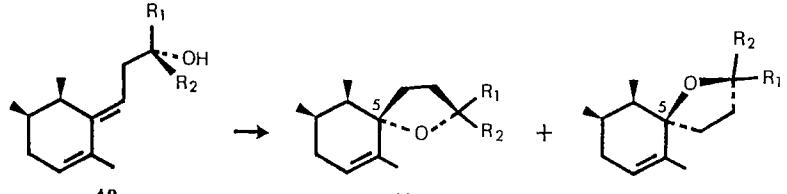
The synthesis of the eight possible diastereoisomeric racemates of dactyloxene-B (44) has been carried out recently by Ohloff and co-workers (15). In the course of this work, they have observed that the spiro bicyclic ethers 46 and 49 are formed more rapidly than their C-5 epimers 47 and 50 respectively on acid cyclization (p-TSA in CH_2Cl_2) of the hydroxy-diene precursors 45 and 48 (R_1= CH_3 and R_2= C≡CH or the opposite configuration).



44

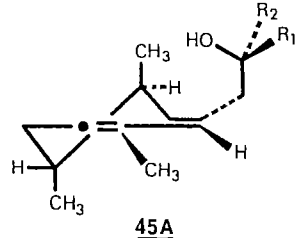


45 46 47

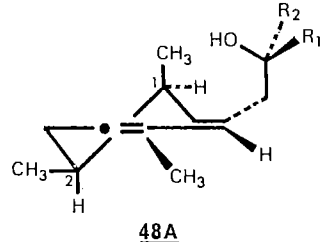


48 49 50

The trans-dimethyl precursors (R_1= CH_3, R_2= C≡CH, or the opposite) are known to exist in conformation 45A where both secondary methyl groups are axially oriented. The cis-dimethyl precursors 48 take conformation 48A which has an equatorial methyl group at C-2 and a pseudo-axial one at C-1.



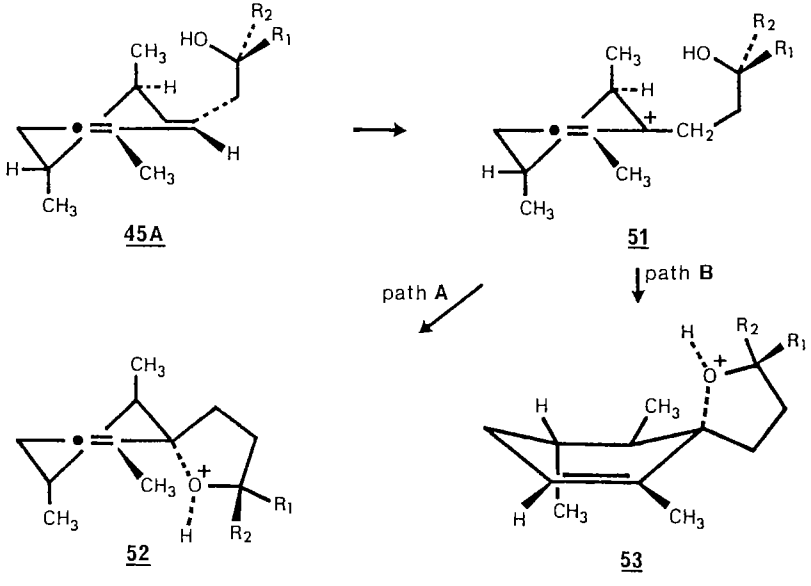
45A



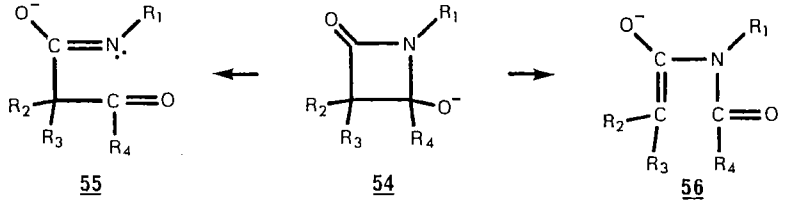
48A

A plausible explanation for the kinetically preferred formation of 46 and 49 can be obtained by taking the principle of stereoelectronic control into consideration: for instance, protonation of 45A should give the allylic

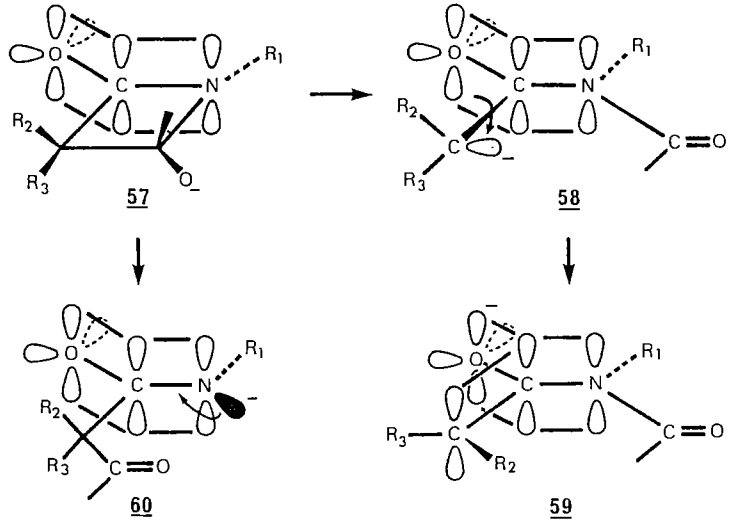
carbonium ion 51. A nucleophilic attack on the bottom face of ion 51 (path A) should be favored over that on the top face (path B) because the former leads a half-chair transition state (52) while the latter leads to a less stable boat-like transition state (53). The preferred formation of 49 from 48A can also be explained in a similar manner.



Ring opening of the β-lactam oxyanion 54 is now considered. Two different ring-openings are possible, a C−N bond cleavage to give 55 or a C−C bond cleavage to form 56. Experimentally, the only process observed is 54 → 55 (16), although theoretical calculations (17) indicate that intermediate 56 is more stable than 55.



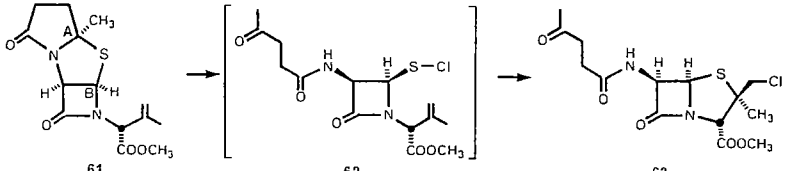
Kikuchi (16) has proposed that the experimental result can be readily explained because the process 54 → 56, by comparison with the process 54 → 55, is unfavorable from the stereoelectronic point of view. The C−C bond breaking process (54 → 56) may be expressed by a two-stage mechanism (57 → 58 → 59). In the first stage, the carbanion produced (58) is of high energy (no overlap) and the stabilization is achieved by the 90° rotation about the C−C bond (→ 59). Thus even if the C−C bond breaking and the C−C bond rotation occur concertedly, the negative charge developing at the carbon atoms is not largely stabilized at the transition state as the overlap between the negative charge and the carbonyl π system is small.



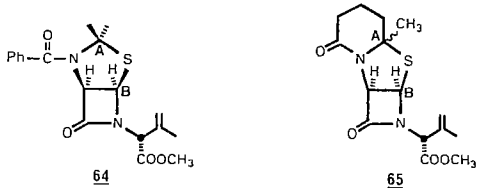
On the other hand, cleavage of the C−N bond gives directly the stabilized amide ion 60. In the ion 60, one nitrogen electron pair (p-orbital) is delocalized through a n-π* interaction (primary electronic effect) while the other is delocalized by an n-σ* interaction (secondary electronic effect; indeed, the newly generated electron pair is antiperiplanar to the C−O σ bond of the carbonyl function). Thus, both electron pairs of the nitrogen atom are delocalized.

Treatment of tricyclic β-lactam 61 which t-butyl hypochlorite in wet THF provided β-chloromethylpenam 63 (18). This 55% yield conversion takes place

presumably through the intermediacy on the sulfenyl chloride 62. Thus, specific cleavage of the $C_A - S$ in preference to the $C_B - S$ bond is observed in 61. Contrary to this result, preferential cleavage of the $C_B - S$ bond takes place with the bicyclic ß-lactam 64 (19). Similarly, neither of the tricyclic diastereoisomers 65 provided the selective $C_A - S$ bond cleavage (18).

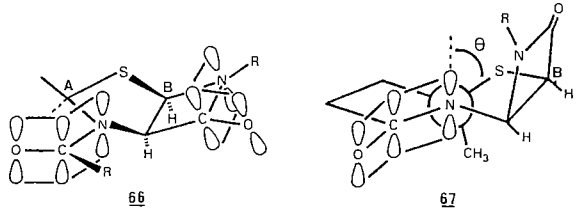


61 62 63



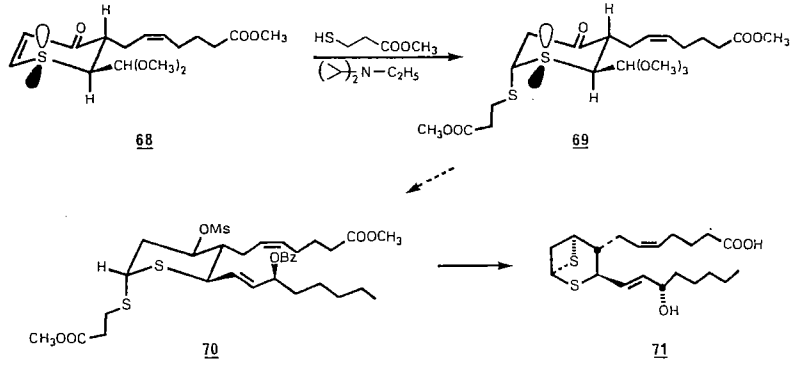
64 65

Baldwin and Christie (18) have proposed that the origin of this difference almost certainly derives from a stereoelectronic factor. In 64 and 65, the $C_B - S$ bond is more nearly orthogonal to the ß-lactam amide plane than the $C_A - S$ bons is, with respect to the thiazolidine amide plane (cf. 66). The $C_B - S$ bond is therefore weaker than the $C_A - S$ bond and is preferentially cleaved. With tricyclic ß-lactam 61, due to the five-membered ring, the $C_A - S$ bond becomes more nearly orthogonal to the thiazolidine amide plane (cf. 67). As a consequence, the ordering of bond lability is reversed and the $C_A - S$ bond is cleaved more readily. The stereoelectronically controlled step 61 → 63 has led to a stereospecific synthesis of a penicillin derivative from a peptide precursor.



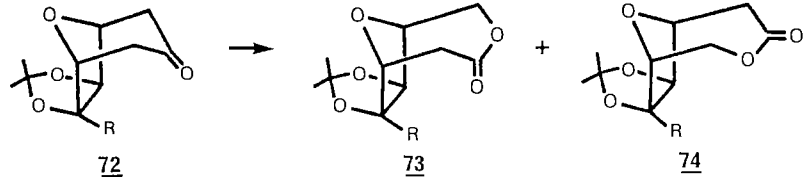
66 67

Ohuchida, Hamanaka, and Hayashi (20) have reported a synthesis of the dithia-analogue 71 of tromboxane A. In one of the key steps, the stereoelectronically controlled axial conjugate addition of methyl 3-mercaptopropionate to 68 was realized with stereoselectivity by using diisopropylethylamine (0.2 equiv) in DMF. The product obtained 69, was then converted into 70 which was further transformed into the desired dithio derivative 71 [(a) t-BuO^-K^+, HMPA, 25°C; (b) $NaOCH_3$, CH_3OH; (c) NaOH 0.2 N, THF].



68 69 70 71

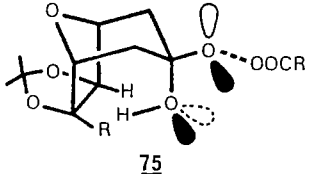
Noyori, Kobayashi, and Sato (21) have reported the Baeyer-Villiger oxidation (22) of the substituted oxabicyclooctanones 72 (R= CH_3, n-C_5H_{11}, C_6H_5 or CH_2OR) with trifluoroacetic acid. They found that lactones 73 were produced in a larger proportion (≈2:1 to ≈3:1) than the isomeric lactones 74.



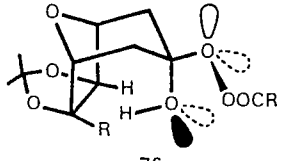
72 73 74

The preferred formation of lactone 73 was explained by the orientation of the non-bonded electron pairs of the hydroxyl group in the corresponding tetrahedral intermediate and by assuming that the migrating C — C bond must be antiperiplanar to the RCOO — O bond. They have also assumed that the peracid reacts on the least hindered face of the carbonyl group in 72.

Under such conditions, only four different conformations are possible (75, 76, 77, and 78) for the tetrahedral intermediate. Conformations 75 and 76 are eliminated on the basis of steric interactions between the hydroxyl hydrogen and the five-membered ring. Also, conformation 77 should be less stable than conformation 78 because the former has a steric interaction between the R group and the hydroxyl hydrogen. On that basis, the preferred formation of lactone 73 (from 78) over lactone 74 (from 77) would be due to a combination of steric and stereoelectronic effects. This rationalization is based on the reasonable assumption that an electron pair of an oxygen atom is a better electron donor than an O—H bond. This is the first rationalization which points out the importance of the stereochemistry of an hydroxyl group (relative orientation of the oxygen electron pair and the hydrogen atom with the remaining reacting bonds) in order to explain an experimental result.



75



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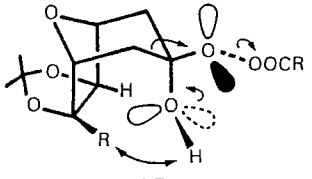

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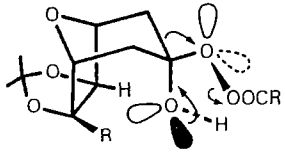
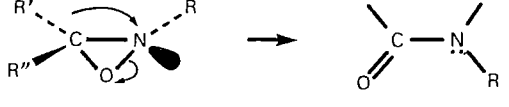


78

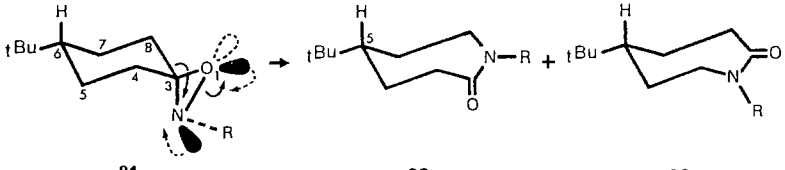
Lattes and co-workers (23) have studied the photochemical and thermal rearrangement of oxaziridines into amides (79 → 80).



79 80

They have obtained unambiguous evidence that the photochemical process is completely regiospecific. They have further concluded that this process must be controlled by stereoelectronic factors because the bond (R' — C) which is anti to the nitrogen lone pair in oxaziridine 79 migrates more easily than the bond (R"— C) which is syn to the lone pair. Syn-anti isomerization by nitrogen inversion in oxaziridines 79 was rigorously excluded under the reaction conditions (r.t.).

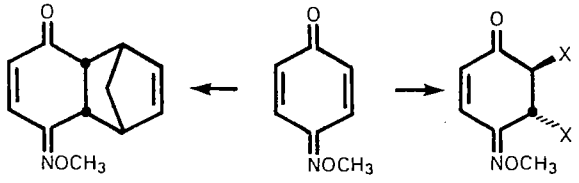
Their key experiment is the following: optically active oxaziridine 81 (100% optical purity) was synthesized and its absolute configuration was established. The photolysis of 81 gave the optically active lactam 82 (having an S configuration at C-5) in 80% yield; none of the enantiomer 83 was observed. The driving force for the migration must therefore be the two electron pairs (one from the nitrogen and one from the oxygen atom) which are antiperiplanar to the C_3-C_8 bond.



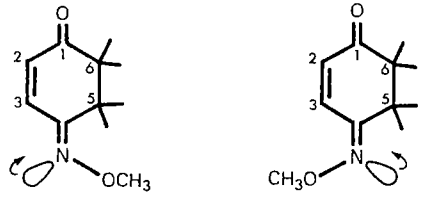
81 82 83

They have further pointed out that the lower regioselectivity observed in the thermal rearrangement of oxaziridines does not rule out the above stereoelectronic requirement. In this case, the energy required for the reaction in sufficient to induce both nitrogen inversion in the starting oxaziridine and migration of the C-substituents.

Baldwin and Norris (24) have reported a study on the kinetically controlled addition of halogen (bromine or chlorine) or cyclopentadiene to 1,4-benzoquinone 4-(O-methyloxime) (84 → 86 and 84 → 85). The most remarkable result of the above addition reactions is the overwhelming predominance of products which have the configuration 87, where the methoxy group is anti to the remaining double-bond, rather than the alternative arrangement 88; in the case of either bromine and chlorine, over 70% of configuration 87 is produced and with cyclopentadiene, this arrangement is observed in excess of 93%.

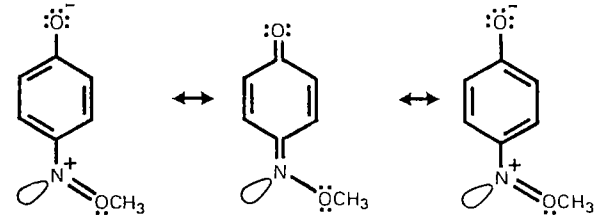


85 84 86



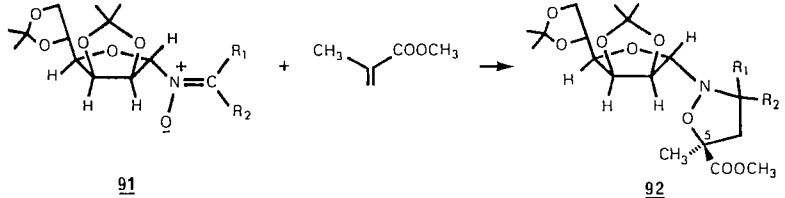
87 88

The authors have explained these results by invoking a stereoelectronic effect which involves the nonbonding electrons on the oxime nitrogen. They have proposed that the nonbonding electrons on the nitrogen atom of the oxime group exert a subtle but significant effect on the benzene sigma C—C bond which is oriented antiperiplanar. This $n \rightarrow \sigma^*$ interaction will produce some antibonding character in the antiperiplanar C—C bond with concomitant lengthening of the bond. Thus, in structures 87 and 88, the bonds being lengthened are those syn to the oxime substituent, i.e. C_4-C_5 and C_3-C_4 respectively. Lengthening of the C_3-C_4 bond in 88 will reduce the effective p-p orbital overlap between carbon atoms 3 and 4, reducing in turn the delocalization of the lone pair on the oxime oxygen atom, through the conjugated system, onto the carbonyl oxygen. The bond lengthening occurring in 87 does not lead to a reduction of electronic delocalization; this configuration is therefore more stable than 88. It is also a logical consequence of this proposal that in quinonoid derivatives like 84, the canonical structure 89 makes a greater contribution than structure 90. This is in accord with the hypothesis suggested by Norris and Sternhell (25-28) to explain the ^1H nmr coupling constant and the position of syn-anti equilibrium in these derivatives.

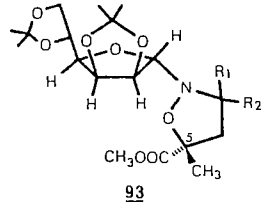


89 90

Vasella and collaborators (29-31) have reported that the cycloaddition of nitrones 91 ($R_1=R_2=H$; $R_1=CH_3$, $R_2=H$; $R_1=H$, $R_2=CH_3$) to methyl methacrylate yields diastereoisomeric adducts 92 and 93 which differ at C-5. For instance, the nitrone 91 ($R_1=R_2=CH_3$) gave a 95:5 mixture of 92 and 93 ($R_1=R_2=CH_3$). Vasella has suggested that the observed stereoselectivity is due to a stereoelectronic effect which strongly influences the stereochemistry of the transition state of the cycloaddition reaction. This stereoelectronic effect is caused by the nitrogen electron pair which is oriented antiperiplanar to the C—O bond of the furanose ring during the cycloaddition reaction (cf. 94 → 95). When this additional electronic delocalization is operative, the energy of the transition state is lowered accordingly.



91 92



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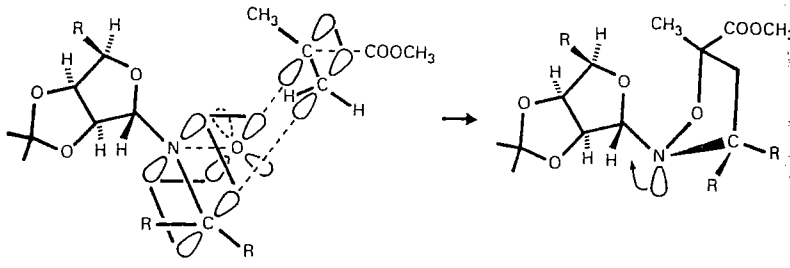
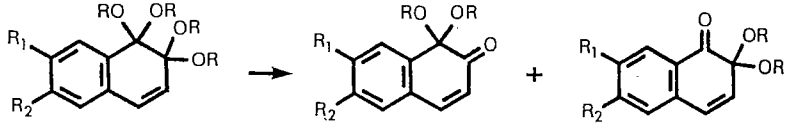
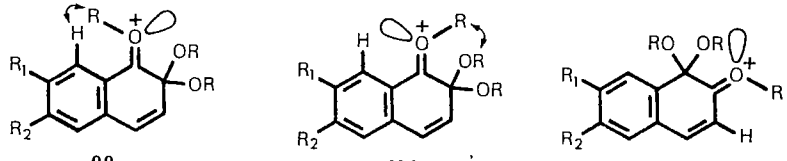


94 95

Dolson and Swenton (32) have found that the acid hydrolysis of bisketals 96A and 96B (R=CH_3) is highly regiospecific yielding monoketals 97A and 97B respectively. On the other hand, bisketal 96C (R=CH_3) gave a ≈3:1 mixture of 97C and 98C. The selectivity observed in the hydrolysis of 96A and 96B was ascribed to the preferential formation of the linearly conjugated oxonium ion 101 relative to the cross-conjugated oxonium ions 99 and 100. Also, as the transition state for conversion to the oxonium ion is approached, most effective stabilization of the positive charge requires the alkoxy group to be in the plane of the ring. For 99 and 100, this planarity generates steric congestion while for 101, this planar arrangement is quite acceptable sterically. For bisketal 96C, the formation of a mixture of monoketals 97C and 98C is apparently due to additional stabilization of the p-methoxy group in cations 99 and 100.

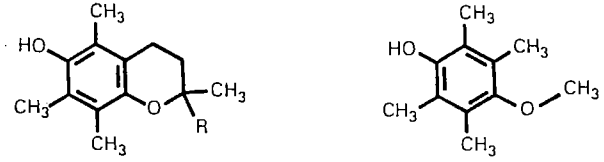


96A $R_1 = R_2 = H$ 97A 98A
96B $R_1 = OCH_3$, $R_2 = H$ 97B 98B
96C $R_1 = H$, $R_2 = OCH_3$ 97C 98C



99 100 101

Burton, Le Page, Gabe, and Ingold (33) have recently proposed that the superior antioxidant activity of vitamin E (102) and the related phenol 103 by comparison with 4-methoxy-2,3,5,6-tetramethylphenol (104) is due to ster-

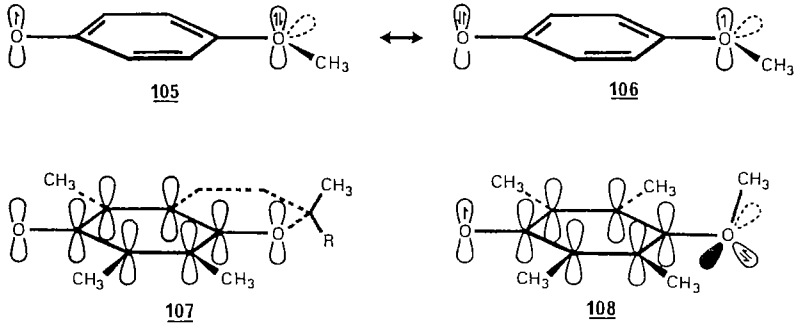


102 R= $(CH_2CH_2CH_2CH(CH_3))_3CH_3$ 104
103 R= CH_3

oelectronic factors. The antioxidant activity of phenols depends on their capacity in trapping radicals as shown in the following equations.

$$ROO\cdot + ArOH \longrightarrow ROOH + ArO\cdot$$
$$ROO\cdot + ArO\cdot \longrightarrow \text{nonradical products}$$

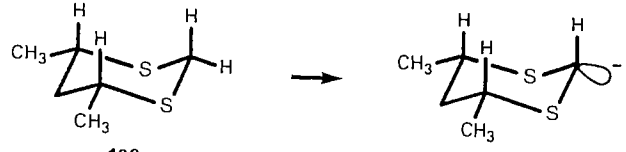
With 4-methoxyphenols, the phenoxyl formed is further stabilized by delocalization of the unpaired electron to the p-type orbital of the methoxyl oxygen (105 ↔ 106). This interaction is allowed in vitamin E and in compound 103 but prohibited in compound 104 because the former two compounds exist in conformation 107 and the latter in conformation 108. In conformation 108, due to the methyl groups in ortho position, the methoxyl group is twisted out of the plane of the aromatic ring and the delocalization of the methoxyl oxygen electron pair is consequently prohibited.



105 106 107 108

Hydrogen atoms at carbon next to sulfur tend to be acidic (34); carbanions can therefore be generated under appropriate basic conditions with sulfides, sulfoxides and sulfonium salts. It was also observed that the acidity depends

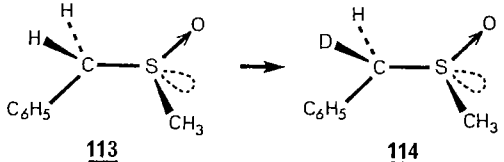
on the stereochemistry of the C−H bond. For instance, Eliel and collaborators (35-39) have shown that the equatorial carbanion 110 derived from 1,3-dithiane 109 is thermodynamically more stable than the axial isomer 111. Carbanion 110 is also preferentially generated from 109 under kinetically controlled conditions and its reaction with electrophiles is stereocontrolled yielding the equatorial product 112 (E= H or alkyl). The stereoelectronic effect has also been demonstrated in 1,3-oxathianes (40) and in 1,3-dioxanes (41).



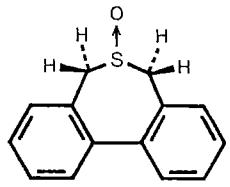
109 110

111 112

Wolfe and co-workers (42) were the first to observe the preferential exchange with D_2O/OD^-, of one of the diastereotopic benzylic hydrogen in benzyl methyl sulfoxide. Baldwin and co-workers (43) then showed that the deuterium exchange of the kinetically more labile benzylic proton in (S)-benzyl methyl sulfoxide (113) yields the (R)-configuration 114. The sulfoxide case has since been investigated extensively (44-47). Considerably greater selectivity (rate ratio of over 1000) was found in the H/D exchange and the alkylation of benzyl t-butyl sulfoxide (48, 49) and the exchange of the α-hydrogens in the bridged biaryl sulfoxide 115 (50). There is also



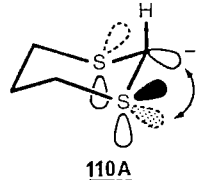
113 114



115

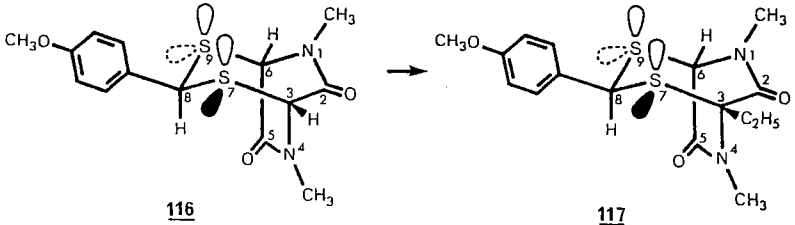
strong evidence that the acidity of the protons alpha to the sulfonium group depends upon the orientation of the C−H bond with respect to the substituent on the sulfur atom (51-53).

It can be concluded from these results that powerful stereoelectronic effects control the acidity in these compounds. There remains however to understand the nature of these effects. Several reports (54-61) indicate that the enhanced acidity of C−H alpha to sulfur is not due to a (d-p)π stabilization of the carbanion by the d orbitals on sulfur (62, 63). This electronic effect has been referred to (64) as the "gauche effect" which would be a tendency to adopt a structure which has the maximum number of gauche interactions between the adjacent electron pairs and/or polar bonds. Lehn and Wipff (61) have carried out an ab initio study which shows that carbanion stabilization by α-heteroatoms is subject to appreciable stereoelectronic effects. Their calculations have shown that equatorial type carbanions (cf. 110) are much more stable than axial type carbanions (cf. 111). According to these authors, these stereoelectronic effects may be interpreted in terms of a destabilizing interaction in 111 (mixing of two occupied orbitals) and a stabilizing interaction in 110 (C^- lone pair mixing with the antibonding α* C−S orbital, cf. 110A). Theoretical work from Lehn, Wipff, and Demuynck (65) indicates that α-seleno carbanions are subject to appreciable stereoelectronic effects similar to those of α-thia carbanions.



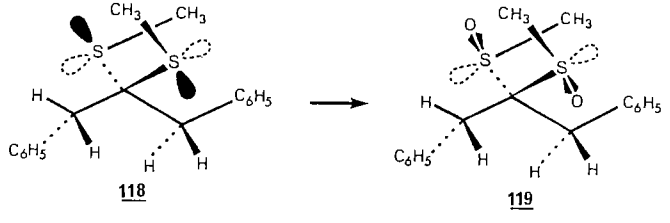
110A

Kishi and collaborators (66-68) have observed a regiospecific metallation (n-BuLi, THF, -78°C) and alkylation with ethyl iodide of anisylidenedithio-N,N'-dimethylpiperazine-2,5-dione (116 → 117). This result leads to the conclusion that H_3 is more acidic than the H_6 in 116 and that the relative acidity of these two bridgehead hydrogens must depend on stereoelectronic effects. An X-ray structure determination (69) shows that the dihedral angle $C_8-S_9-C_6-H_6$ (154°) is close to that for $C_8-S_7-C_3-Et$ (155.7°); it is therefore difficult to attribute the regiospecificity to a difference in overlap between the sulfur 3d orbitals and the sp^3 orbital at the bridgehead positions. Kishi has suggested that the regiospecificity could arise from the different environments around the lone pairs of the sulfur atoms. Indeed, the relative orientation of the two lone pairs of S_7 with the C_3-C_2 and C_3-N_4 bonds is completely different from that of S_9 with the C_6-C_5 and C_6-N_1 bonds. However, the nature of these stereoelectronic effects which make H_3 more acidic remains to be understood.



116 117

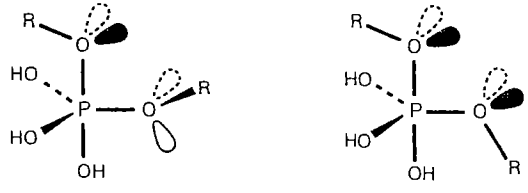
The reaction of thioacetals with two equivalents of peroxy acids generally affords epimeric gem-disulfoxides, the ratio of epimers being subject to kinetic and/or equilibrium control (70). However, Poje, Sikirica, Vicković, and Bruvo (71) have reported the first example of a stereospecific oxidation in the gem-disulfide series. They found that 2,2-bis(methylthio)-1,3-diphenylpropane is smoothly oxidized to the corresponding meso-disulfoxide with m-chloroperbenzoic acid. The study of conformational properties in solution by nmr indicated that the meso-disulfoxide exists in conformation 119 which



118 119

is the same as that found in the solid state by X-ray analysis. The above authors have suggested that the configuration and conformation of meso-disulfoxide 119 is the result of a stereospecific oxidation of conformation 118 of the gem-disulfide. They have further suggested that this particular stereochemical course cannot be explained by steric effects; it must have an electronic origin.

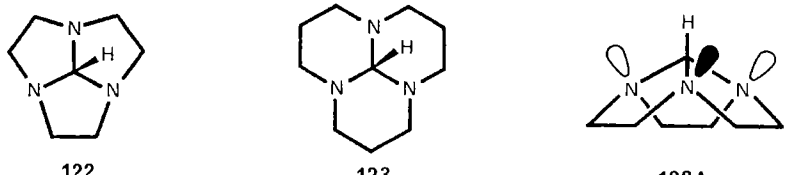
Lehn and Wipff (72) and Gorenstein and co-workers (73-80) have proposed on the basis of molecular orbital calculations that stereoelectronic effects similar to those observed in esters and amides play also an important role in the hydrolysis of phosphate esters. For instance, calculations suggest that the axial P — OR bond in the trigonal bipyramid conformation 120 is weaker than that in the conformation 121 because in the former, the oxygen atom of the equatorial OR group has an electron pair antiperiplanar to the axial P — OR bond. Experimental results tend to support this interesting proposal but additional experiments are needed before unambiguous conclusions can be reached (81).



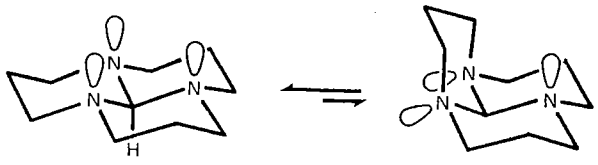
120 121

Unusual reactivity

Very unusual reactivity has been observed (82-84) with the tricyclic orthoamides 122 and 123. This can be readily explained on the basis of the stereoelectronic effects due to the three nitrogen electron pairs.



122 123 122A



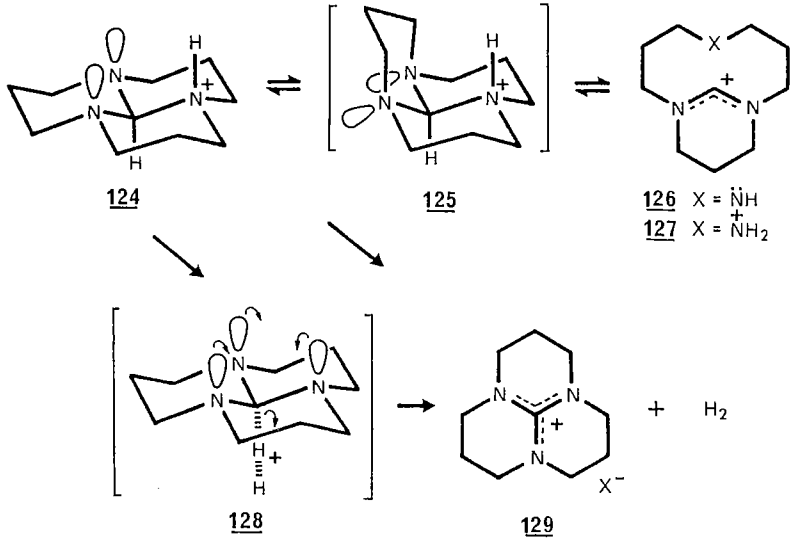
123A 123B

Orthoamide 122 adopts a conformation (122A) in which the electron pairs are synperiplanar (or nearly) to the central carbon-hydrogen bond. This is confirmed by pronounced deshielding of the central hydrogen atom (δ=5.0 ppm) in the ^1H nmr spectrum and by the absence of Bohlmann bands (85, 86) in the infrared spectrum. The orthoamide 123 adopts conformation 123A which has the nitrogen lone pairs antiperiplanar to the central C – H bond. Low temperature ^{13}C nmr analysis indicates that this conformer must predominate over conformer 123B which is stabilized by two anomeric effects (two electron pairs antiperiplanar to a C – N bond) but destabilized by steric effects. The six equivalent axial carbon-hydrogen bonds adjacent to the nitrogens in conformer 123A are responsible for strong Bohlmann bands between 2690 and 2800 cm^{-1} in the infrared spectrum. Furthermore, an additional Bohlmann band due to the central C – H bond appears at 2450 cm^{-1}, an extraordinarily low frequency. In the monodeuterated derivative 123 (H=D), this absorption is absent, and a new band appears near 1800 cm^{-1}. The positions of Bohlmann bands are therefore influenced by stereoelectronic effects.

The chemical shift of the methine proton in orthoamide 123 is 2.3 ppm. It is therefore at a much higher field than that of orthoamide 122. This remarkable difference of 2.7 ppm can be ascribed to a dramatic stereoelectronic effect. The origin of the unusual spectroscopic properties of orthoamide 123 presumably is the antiperiplanar relationship of the central C – H bond to the three lone pairs. This arrangement permits mixing of the lone pair orbital with the antibonding orbital of the central C – H bond (σ^*). As a result, the electron density at the methine hydrogen increases and the central C – H bond is weakened. Indeed, this hydrogen has a notably small chemical shift.

The orthoamides 122 and 123 are therefore completely different: one adopts a conformation in which the central C – H bond is synperiplanar to the adjacent lone pairs (122A) while the other takes a conformation in which the central C – H bond is antiperiplanar (123A). These two compounds are therefore expected to have quite a different reactivity.

Treatment of orthoamide 123 with equimolar amounts of aqueous hydrochloric acid yielded the salt 124 from which 123 can be regenerated by neutralization. NMR indicates that salt 124 and bicyclic formamidinium ion 126 interconvert rapidly at 70°C. This is explained by a conformational change from 124 into 125 which permits elimination of the amine group with stereoelectronic control (125 → 126). Finally, addition of excess hydrochloric acid to orthoamide 123 precipitated the bicyclic dichloride 127.

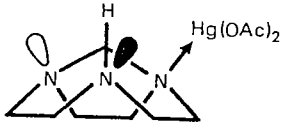


124 125 126 X = $\ddot{N}H$ 127 X = $\overset{+}{N}H_2$

128 129

Pyrolysis of tetrafluoroborate orthoamide salt 124 under nitrogen cleanly gave guanidinium tetrafluoroborate 129 (X=BF_4^-) under remarkably mild conditions (110°C, 23 h). Molecular hydrogen, the necessary by-product was trapped in 76% yield. Erhardt and Wuest (84) have suggested that this reaction takes place in two steps: (1) dissociation of ammonium tetrafluoroborate 124 into orthoamide 123 and then (2) oxidation of orthoamide 123 by H^+ via a transition state or an intermediate having the linear configuration 128. This remarkable transformation can be rationalized only if the stereoelectronic effects of the three nitrogen lone pairs are taken into consideration (cf. 128).

Orthoamide 123 cleanly reduced mercuric acetate in ethanol at 25°C to mercury or mercurous acetate. The organic product formed is guanidinium salt 129 (X= $^-$OAc). Similarly, iodine in methanolic potassium carbonate at 25°C oxidized orthoamide 123 to guanidinium iodide 129 (X=$^-$I). On the other hand, orthoamide 122 does not react with mercuric acetate even in boiling ethanol. Syn-elimination of mercury and acetic acid from complex 130 must be slow but anti-elimination from complex 131 (Y= I_2 or HgX_2) must occur readily.



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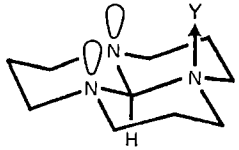

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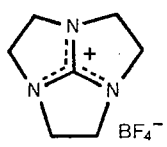
Oxidation of five-membered tricyclic orthoamide 122 to give the strained guanidinium tetrafluoroborate 132 is however possible with triphenylcarbenium tetrafluoroborate. The six-membered tricyclic orthoamide 123 also reduced triphenylcarbenium tetrafluoroborate, but, very surprisingly, only a very small amount (<5%) of the expected guanidinium tetrafluoroborate 129 (X=BF_4^-) was formed. Thus, hydrogen is transferred not from the central carbon atom but from one of the other six equivalent carbon atoms, giving presumably iminium tetrafluoroborate 133 or the isomeric imine 134 as the initial products of oxidation. These intermediates could not be isolated, however, and the final products of oxidation appear to be oligomers of 134 due to a rapid cyclotrimerization characteristic of imines.

The low reactivity of the central carbon-hydrogen bond in orthoamide 123 was explained in two ways (82):

(1) steric factors make a methine hydrogen inaccessible to triphenylmethyl cations or radicals;
(2) the major products of oxidation by triphenylcarbenium may result from the cleavage of carbon-hydrogen bonds gauche or synperiplanar to lone pairs.

Thus, an intermediate similar to ammonium salt 135 would be formed first and it would then undergo a syn-elimination by the loss of H_B to give only iminium ion 133 since the triphenylmethyl group and the methine hydrogen H_A in 135 lie on opposite faces of the molecule.



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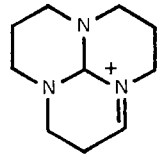

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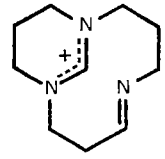

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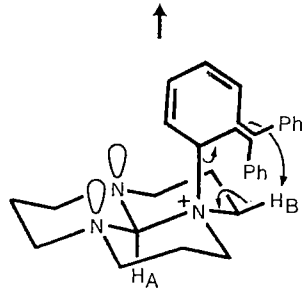

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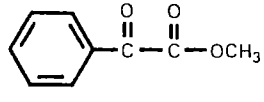
Heating at 165°C for 12 h, equimolar amounts of magnesium perchlorate hemihydrate, five-membered orthoamide 122 and methyl phenyl glyoxalate (136) produced guanidinium perchlorate 132 (BF_4^- = ClO_4^-) and hydrolysis of the crude product provided mandelic acid (137) in 45% yield. Six-membered orthoamide 123 also reduces methyl phenyl glyoxalate to mandelic acid. The predominant product of oxidation was again the perchlorate salt of the oligomer obtained previously from imine 134.



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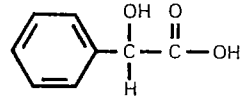

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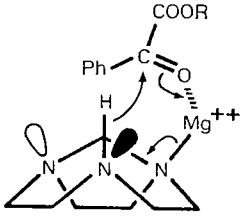
The magnesium cation is essential in these oxidation reactions. Several plausible mechanisms which provide a role for the magnesium cation and which account for the absence of guanidinium ion 129 are possible. One of them proposed by Wuest and collaborators (82) is the direct transfer of a proton and two electrons within intermediates similar to the complexes 138 and 139.



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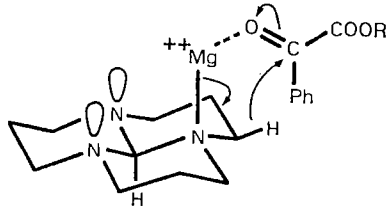
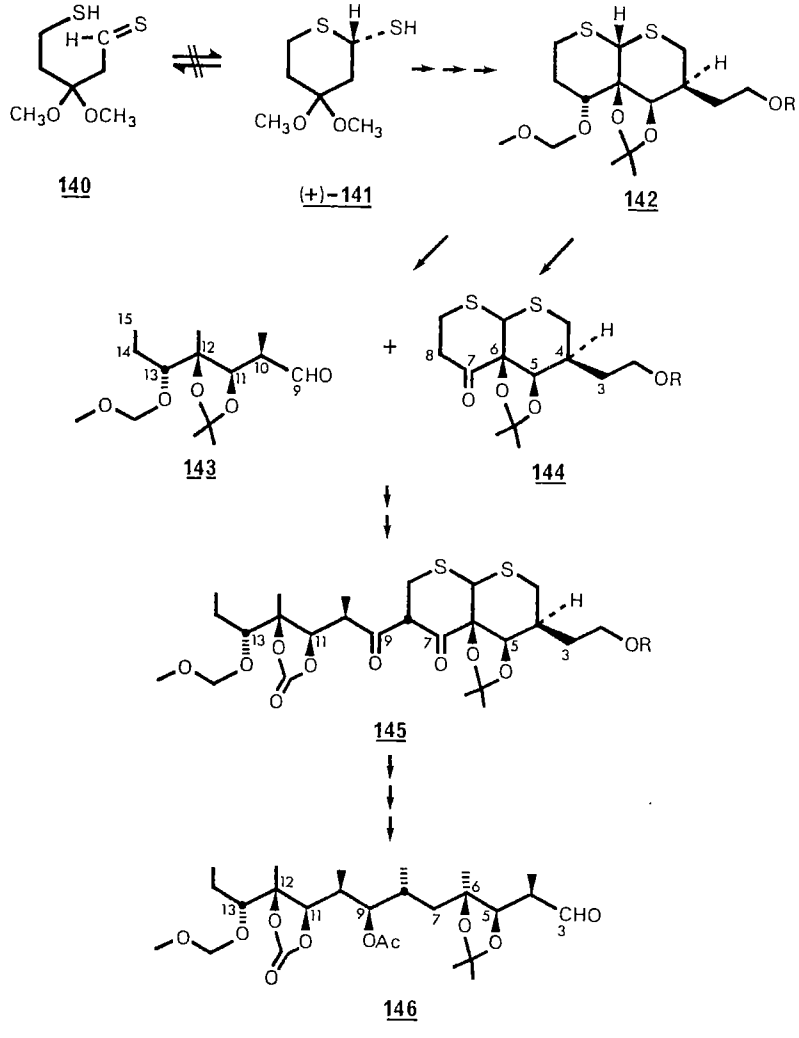


139

New strategy in organic synthesis

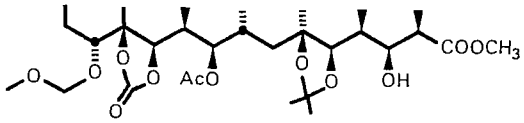
In the total synthesis of optically active erythromycin A reported by Woodward and collaborators (87), the bicyclic compound 142 (Fig. 1) was used to produce the two segments C_9-C_{15} (143) and C_3-C_8 (144) of erythronolide A. These two segments were then combined (→145) and converted into 146). Aldol condensation of a propionate ester derivative with 146 gave the erythronolide A secoacid derivative 147 (Fig. 2) which was successfully transformed into erythromycin A (149) through a series of chemical transformations where compound 148 was one of the key intermediates.

Interestingly, the optically active dithiadecalin 142 was prepared through several steps starting with the optically active (+)-tetrahydrothiopyranthiol 141 which contains only one chiral center. As a first operation, racemic 141 was converted into a mixture of two diastereoisomeric thioesters by reaction with (-)-camphanylchloride and the desired optically active thioester of (+)-141 was isolated by crystallization. Optically active (+)-141 was then obtained from the optically active thioester by treatment with sodium methoxide in methanol. It is remarkable that (+)-141 did not racemize under neutral and even strongly basic conditions. Indeed, the "normally anticipated" equilibrium 140 ⇌ 141 did not take place. This unexpected result is probably rooted in some stereoelectronic factor which is not yet understood. Compound (+)-141 was used twice in the course of the synthesis (to produce 143 and 144) and its only chiral center was destroyed twice in order to produce the two methyl groups at C-6 and C-12 (cf. 146). Furthermore, it is interesting to point out that the chirality of (+)-141 is responsible for the control of the relative and absolute stereochemistry of all the asymmetric centers of erythronolide A. This is indeed a very ingenious strategy.



140 (+)-141 142 143 144 145 146

Fig. 1



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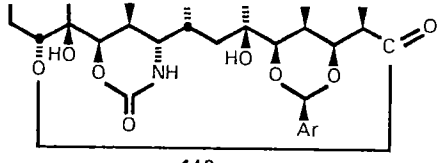

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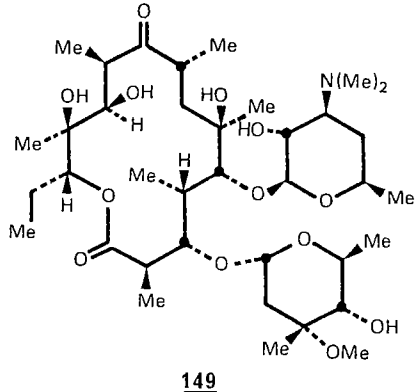

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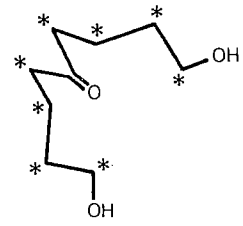
Fig. 2

A new strategy for the synthesis of erythromycin A and closely related macrolide antibiotics was elaborated in our laboratory (88). This new approach to synthesis is based on the knowledge that stereoelectronic effects control the conformation of acetals. The strategy is based on the 1,7-dioxaspiro-[5.5]undecane system which was found to be conformationally rigid, existing in conformation 150 only (see Chapter 2). This is so because in this conformation, steric effects are at their minimum and the acetal function has

150



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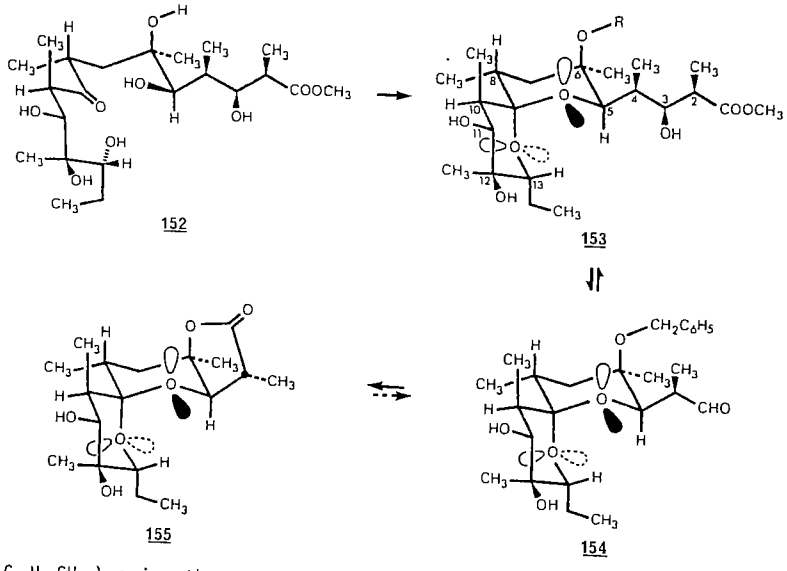
the maximum (stabilizing) stereoelectronic effects (two anomeric effects). Consequently, the spirosystem 150 can be viewed as an aliphatic chain of nine carbon atoms which is locked rigidly in space by the acetal function. The spiro system 150 can therefore be used as a template to introduce several chiral centers with a high degree of control. Indeed, this spirosystem has a potential for the creation of up to eight asymmetric centers (C*), and on hydrolysis, it should yield a dihydroxyketone aliphatic chain (cf. 151), containing the same number of chiral centers.

Erythromycin A (149) was chosen as the target molecule because its structure fits admirably well with the above strategy. Indeed, the methyl ester of the ring-opened form of erythronolide A, the aglycone part of erythromycin A, can be drawn as shown by structure 152. It can be readily seen using molecular models that 152 is an appropriate "dihydroxyketone" which can be converted into the substituted 1,7-dioxaspiro[5.5]undecane 153 (R=H), where the stereoelectronic effects of the spiroacetal are maximum. It is also important to note that seven (C_5, C_6, C_8, and $C_{10} - C_{13}$) of the ten chiral centers of erythronolide A are now part of the two spirorings. Furthermore, the substituents at C-5, C-8, C-10, C-11, and C-13 are all equatorially oriented and the tertiary hydroxyl group at C-6 is axial while that at C-12 is equatorial. Thus, the spirocompound 153 has no undesirable strong steric interactions and it should be readily made both from erythromycin A and by total synthesis. The reconversion of 153 into erythromycin A would then complete the synthesis. This was the plan.

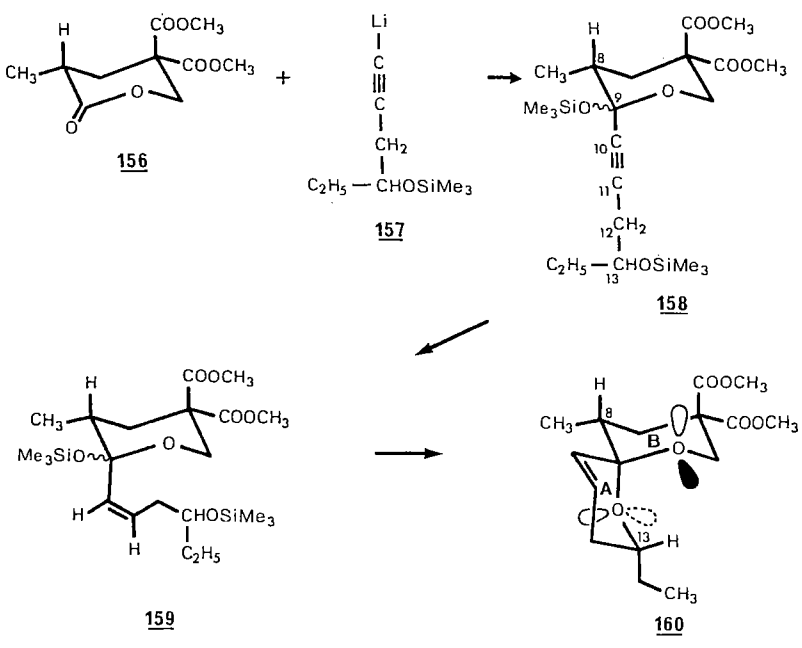
The progress made using this approach follows. Erythromycin was successfully converted into the spirocompound 153 (R=$C_6H_5CH_2$) through a multistep sequence. Compound 153 obtained in this manner was used for testing the end of the synthetic plan. Degradation of the side chain of 153 (R=$C_6H_5CH_2$) gave the aldehyde 154. Compound 154 was then reconverted into spiro 153 (R=



152 153 155 154

$C_6H_5CH_2$) using the methodology developed by Evans and McGee (89), i.e. via an aldol condensation using the zirconium enolate of methyl propionate. In this condensation, two diastereoisomers were formed in a 10:1 ratio and the major isomer was the desired 153 (R=$C_6H_5CH_2$). Therefore, the control of the stereochemistry of two (C-2 and C-3) of the three chiral centers of the side chain of the spiroketal 153 is solved. The spiroaldehyde 154 was also converted into the spirolactone 155 which has all the substituents fixed rigidly in space. The next successful operation was the total synthesis of spirolactone 155.

Lactone 156 which is readily made was chosen as starting material. Condensation of 156 with the lithium acetylide 157 gave after treatment with trimethylsilyl chloride the adduct 158. Synthons 156 and 157 have each one chiral center; their condensation leads to the formation of a diastereoisomeric mixture, but this is irrelevant as two (C-8 and C-9, using erythromycin numbering system) of the three chiral centers in 158 are epimerizable. Controlled catalytic hydrogenation of 158 gave the cis olefin 159. Removal of the trimethylsilyl protecting groups and cyclization to a mixture of spiroisomers ($(CH_3)_3SiOSO_2CF_3$ in CH_2Cl_2) followed by equilibration (pyridinium tosylate in refluxing dichloroethane) gave one single spiroproduct having structure 160 in good yield.

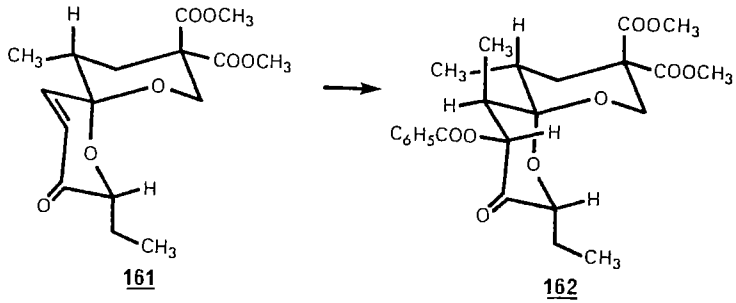


156 157 158 159 160

In compound 160, the ethyl side chain at C-13 is in the equatorial orientation to avoid a strong 1,3-diaxial steric interaction with ring B. Then, stereoelectronic effects of the acetal function adjust the stereochemistry of the two oxygen atoms of the rings. The secondary methyl group at C-8 is epimerizable under acid conditions; as a result, this group takes the equatorial orientation in order to avoid a strong 1,3-diaxial steric interaction with the axial carbomethoxy group. Consequently, only isomer 160 is obtained after equilibration and a complete control of the relative stereochemistry at C-8 and C-13 is achieved. Utilizing the appropriate optically active synthon 157 should give optically active 160 having the absolute configuration corresponding to that of erythromycin.

Compound 160 was then transformed into the conjugated enone 161. Lithium dimethylcopper 1,4-addition on enone 161 and reaction of the resulting enolate with dibenzoyl peroxide gave compound 162 in good yield. Reaction of 162 with methylmagnesium iodide at low temperatures furnished compound 163 again in good yield. Thus by this sequence, an excellent control of

stereochemistry at five chiral centers (C-8, C-10, C-11, C-12, and C-13) of erythromycin A was achieved.



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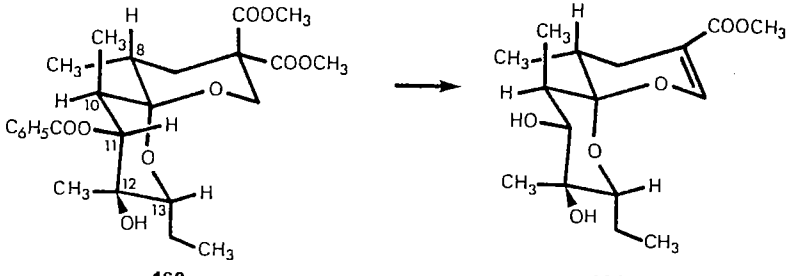
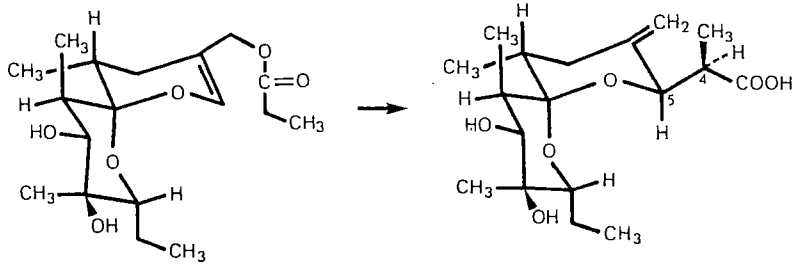


163 164

Through several steps, compound 163 was converted into enolpropionate ester 165 via the conjugated enol ester 164. Using the Claisen rearrangement methodology developed by Ireland and co-workers (90), compound 165 gave a 4:1 mixture of two isomeric products (epimeric at C-4). The major epimer was shown to have structure 166. In this important transformation, two new chiral centers are produced (C-4 and C-5) with the desired configuration. The stereocontrolled introduction of the tertiary hydroxyl group at C-6 was carried out via iodolactonization and hydrogenolysis (166 → 167 → 155). The product obtained was found to be identical in all respects other than optical rotation with spirolactone 155 obtained from the degradation of erythromycin. There now remains to convert spirolactone 155 into spiroaldehyde 154 in order to complete the total synthesis of spiroerythronolide A 153. Work is also progressing for the reconstruction of erythromycin A from spiroerythronolide A 153. This will complete the total synthesis. Interestingly, this new strategy to organic synthesis, based on stereoelectronic principles, permits a control of stereochemistry of all the chiral centers of erythronolide A.



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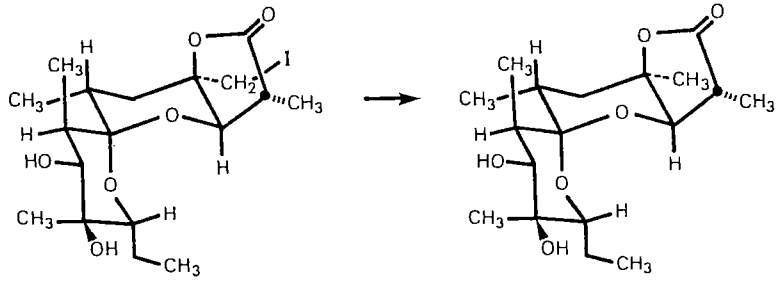

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CHAPTER 9

BIOLOGICAL PROCESSES

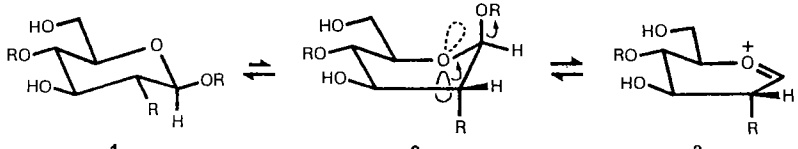
Most of the organic reactions catalyzed by enzymes take place on functionalities which contain heteroatoms. This is the case for the hydrolysis of functional groups such as acetals (e.g. β-galactosidase and lysozyme), esters and amides (e.g. chymotrypsin, trypsin, papain, carboxypeptidase) and phosphate esters (e.g. ribonuclease). This is also true for enzymes which accelerate oxidation-reduction processes (e.g. alcohol dehydrogenase), eliminations, isomerizations, rearrangements, or with reactions that make or break carbon-carbon bonds (e.g. carboxylation, aldol or Claisen condensation, decarboxylation) (1-4). The preceding Chapters have shown that the counterparts to most enzyme catalyzed organic reactions are strongly influenced by stereoelectronic effects when these reactions are carried out with simple reagents. Consequently, there appears to be no doubt that stereoelectronic effects must play an important role in enzymatic catalysis. In fact, these effects must play an even more important role with enzymes as these "highly sophisticated" reagents allow only one among a multitude of chemical transformations.

Indeed, this Chapter will show that the knowledge of transition state stereochemistry for the formation of various enzyme-reaction intermediates is gained through the application of stereoelectronic principles. The driving force of various bond-making or breaking processes and the required conformational changes of some specific enzymic transformations are more clearly understood. The importance of stereochemistry in proton transfer, hydrogen-bonding or metal-coordination also becomes an important parameter. As a result, a much deeper understanding of the events (in three dimensions)

which take place during an enzyme-catalyzed process is gained through the application of stereoelectronic principles.

Enzymatic reactions

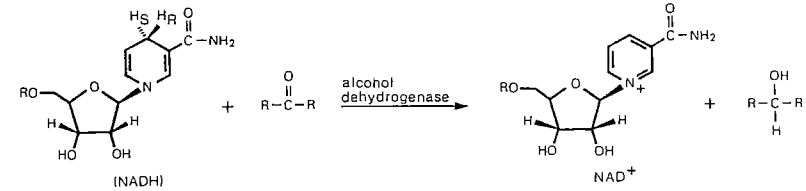
It has been pointed out in Chapter 2 (p. 39) (see also 1-4) that there is good evidence which indicates that in the hydrolysis of β-glycosides by lysozyme, the substrate must take a boat conformation in order to produce the half-chair oxocarbonium ion (1 → 2 → 3). Lysozyme is therefore a good example which provides evidence that stereoelectronic effects play a key role in enzymic hydrolysis.



1 2 3

The alcohol dehydrogenases are zinc metalloenzymes which can oxidize a wide variety of alcohols to their corresponding aldehydes or ketones using nicotinamide adenine dinucleotide (NAD^+) as coenzyme. These reactions are readily reversible so that carbonyl compounds may be reduced by NADH.

These reactions are essentially the result of hydride ion transfer from NADH (4) to the carbonyl compound. The hydrogen transfer is stereospecific and can occur via two different stereochemical pathways depending on the enzyme: one class catalyzes the transfer of the pro-R hydrogen while the other catalyzes the transfer of the pro-S hydrogen (5-7). Benner (8) has recently found that the stereochemical outcome (pro-R and pro-S) depends on the equilibrium constant (K_{eq}) of the reaction. If K_{eq} is less than 10^{-12} M^{-1}, the pro-R hydrogen is generally transferred and if K_{eq} is greater than 10^{-12} M^{-1}, the pro-S hydrogen is transferred. Benner (8) has suggested that



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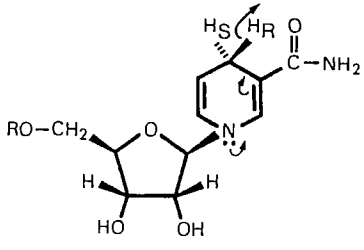
these results indicate that the more reactive carbonyl compounds are reduced by the pro-R hydrogen and the less reactive by the pro-S hydrogen of NADH. He has further suggested that the enzymic transfers of the pro-R and the pro-S hydrogens occur when the nicotinamide ring is in the anti and the syn conformation 5 and 6 respectively. Thus, anti-NADH (5) which delivers the pro-R hydrogen would be a weaker reducing agent than syn-NADH (6) which delivers the pro-S hydrogen. It was further concluded that this difference in reactivity can be explained by taking into account stereoelectronic effects due to the relative orientation of the ring nitrogen electron pair. Interestingly, this idea is supported by experimental data (8).



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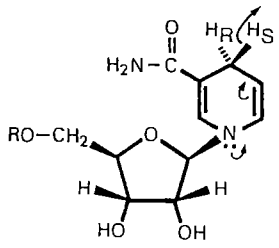
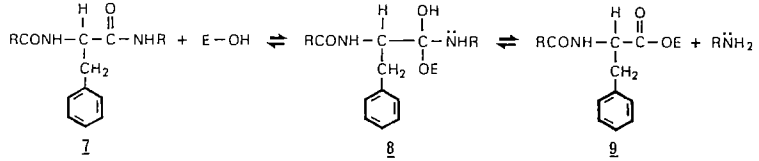


6

The stereochemical aspects of peptide hydrolysis catalyzed by chymotrypsin and related serine proteases has been recently analyzed with respect to requirements for stereoelectronic control of bond cleavage and this analysis has led to a much more complete understanding of the reaction mechanism (9-14).

Chymotrypsin, a serine endopeptidase, most readily reacts at the carboxyl group of the aromatic amino acid residue of proteins and polypeptides (or N-acyl aromatic amino acid esters) to form first a tetrahedral intermediate which then collapses into an acyl-enzyme (7 → 8 → 9). The acyl-enzyme is then hydrolyzed by water to furnish the N-acylated aromatic amino acid again through the formation of a tetrahedral intermediate (10 → 11 → 12) (1-4).



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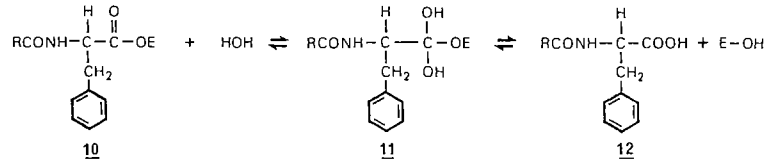
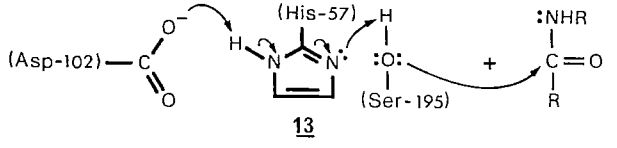


10 11 12

In the above transformation, the hydroxyl group of Ser-195 plays the important role of the nucleophile. The enhanced nucleophilic activity of this group is due to its interaction with Asp-102 and His-57. Indeed this proton relay system (Asp-102 and His-57) through hydrogen bonding makes the Ser-195 hydroxyl group sufficiently nucleophilic to attack the carboxyl function of the substrate with the resulting formation of a tetrahedral intermediate (cf. 13 → 14). Note that this proton relay system is also used to deliver a proton on the nitrogen of the tetrahedral intermediate, a necessary step for the ejection of the amino group in the course of the formation of the acyl-enzyme (cf. 14 → 15).



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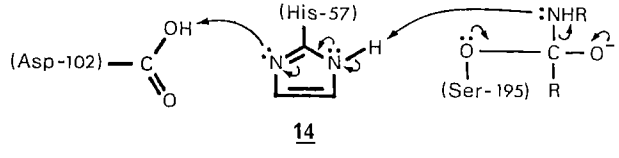

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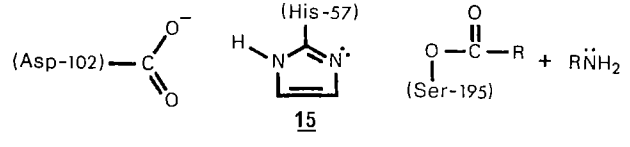


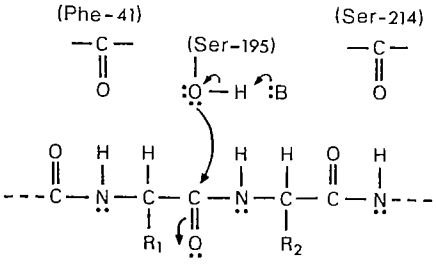
15

In order to confirm and to obtain a more detailed knowledge of the above proposed mechanism, precise information is required on the structure and stereochemistry of intermediates such as the enzyme-substrate complex, the tetrahedral intermediate and the acyl-enzyme. Normally, this information cannot be obtained directly because these intermediates are transient species. On the other hand, it can be obtained indirectly from the precise structural information available from high resolution X-ray diffraction studies of several enzyme derivatives or complexes with substrate analogs.

Using this approach, Bizzozero and Zweifel (9) and Bizzozero and Dutler (10) have constructed molecular models of two intermediates (an enzyme-substrate complex and a tetrahedral intermediate) by appropriate modification of the models of stable enzyme-species. The stable enzyme-species used (15, 16) are trypsin-benzamidine complex (TR-B) (17), trypsin-pancreatic trypsin inhibitor complex (TR-PTI) (18, 19) and tosyl-chymotrypsin (Tos-CHT) (20) which are related to enzyme substrate complex, tetrahedral intermediate and acyl-enzyme respectively.

Comparison of the TR-B, TR-PTI and Tos-CHT models indicates no gross conformational changes in the main chain section carrying the catalytic residues during catalysis. Also, the CH_2OH group of Ser-195 is maintained in one specific conformation but the models show that the imidazole ring of His-57 can take two distinct positions: the in- and the out-positions. More interestingly, in the in-position, the imidazole nitrogen of His-57 can form a good hydrogen bond with the oxygen atom of the hydroxyl group of Ser-195, and in the out-position, the same imidazole nitrogen can form a hydrogen bond with the nitrogen atom of the tetrahedral intermediate derived from the amide nitrogen of the substrate. On that basis, it seems likely that the in- and out-positions are related to the proposed two distinct functional roles of His-57, i.e. 13 → 14 and 14 → 15. It can further be assumed that interconversion of the two positions takes place during catalysis. Interestingly, molecular models suggest that this interconversion takes place with concomitant movement of the backbone part carrying the groups involved (Asp-102 and His-57) in this network of hydrogen bonds.

Model studies suggest also that two CONH groups of the substrate adjacent to the amide function which has reacted to give a tetrahedral intermediate, form a hydrogen bond (CONH···O=C) with the carboxyl oxygens of Phe-41 and Ser-214 (cf. 16 → 17). Thus, formation of these two hydrogen bonds guides the approach of the substrate peptide chain toward a close contact with the enzyme surface.



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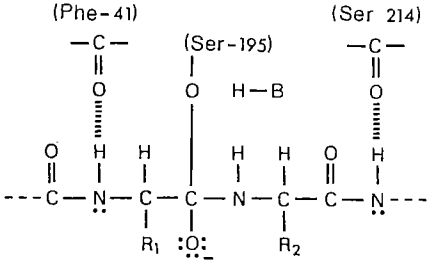
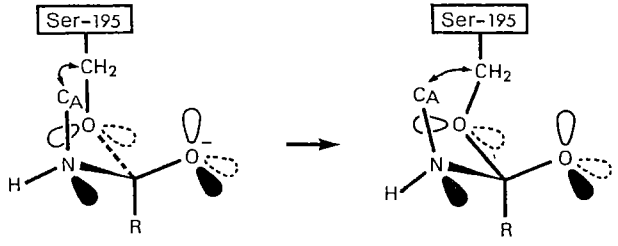


17

It is also interesting to point out that the direction of approach of the Ser-195 hydroxyl group is consistent with the Bürgi-Dunitz approach of nucleophilic attack on carbonyl (21). The only information which cannot be obtained from model building is the relative orientation at the nitrogen atom of the tetrahedral intermediate. This information can however be obtained by application of the principle of stereoelectronic control. Indeed under such conditions, the nucleophilic attack of the hydroxyl group of Ser-195 on the amide function of the substrate leads to a tetrahedral intermediate having the spatial arrangement 18. Final adjustment of the model was then carried out to minimize the strain arising from the 1,3-synperiplanar arrangement between Ser-195 methylene group and the carbon C_A next to the nitrogen in the ideal fully staggered arrangement 18 (see arrow). In the final model (cf. 19), the conformation about these two carbons becomes intermediate between eclipsed and staggered, but the relative orientation of bonds and electron pairs remains essentially the same as in the idealized model 18.



18 19

The complete stereochemical picture for the formation of the tetrahedral intermediate must therefore correspond to 20 → 21 (Fig. 1) where the imidazole ring occupies the in-position. The formation of the acyl-enzyme now requires two changes: (a) the leaving nitrogen of the tetrahedral intermediate must undergo a Walden type inversion (21 → 22) and (b) the imidazole ring of His-57 must then move from the in- to the out-position (22 → 23). Then,

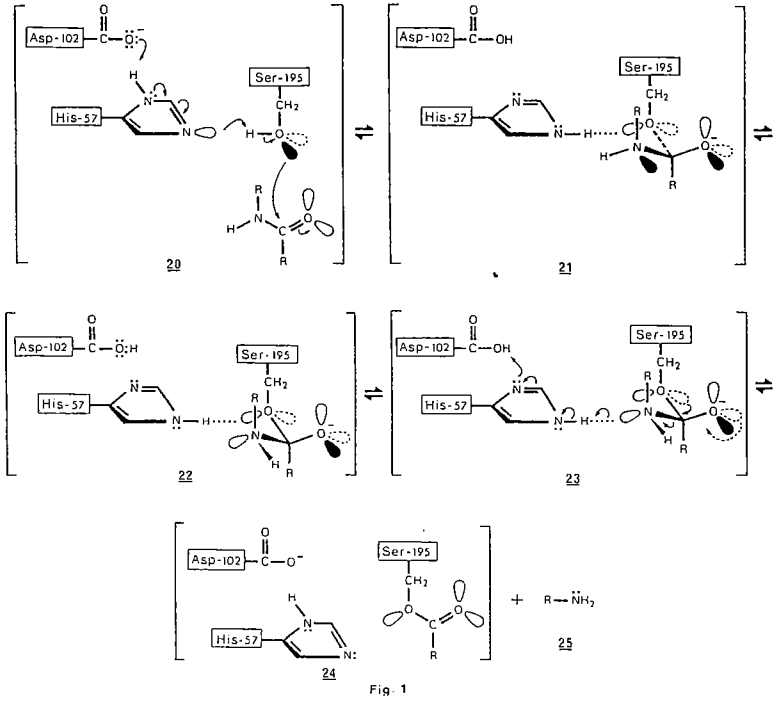


Fig. 1

proton transfer from the imidazole ring of His-57 to the nitrogen atom of the tetrahedral intermediate can take place with concomitant break down to give the acyl-enzyme 24 and the amine 25. Note that this proton transfer can only occur when the electron pair of the leaving nitrogen is oriented toward His-57 (in 22 but not in 21) and that the same proton which is first abstracted from Ser-195 is subsequently donated to the leaving nitrogen.

The hydrolysis of the acyl-enzyme occurs through a similar process where a proton would be abstracted from the entering nucleophile (H_2O) by His-57 which is in the out-position (Fig. 2). This allows the formation of a tetrahedral intermediate (26 → 27). His-57 then moves into the in-position (27 → 28) and delivers a proton to Ser-195. This permits the breakdown of the intermediate to give the free enzyme 29 and the hydrolyzed amino acid residue 30.

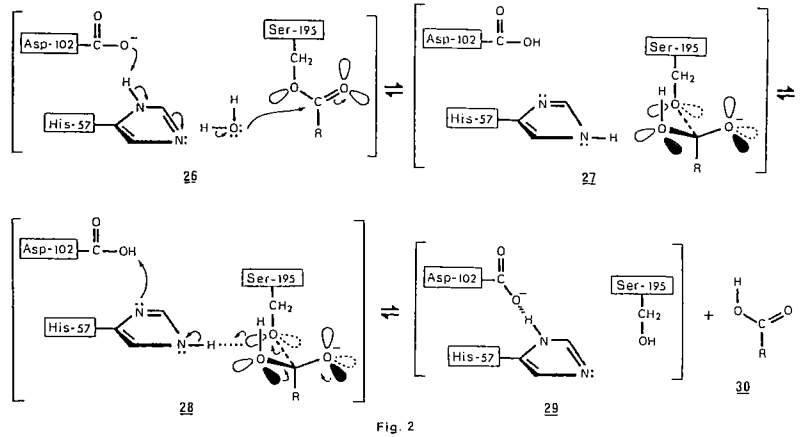
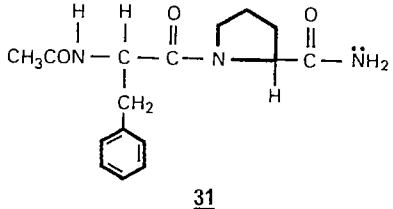


Fig. 2

Returning to the acyl-enzyme process 20 → 24, it is interesting to point out that if the equilibrium between the two tetrahedral intermediates 21 and 23 is on the side of 23 due to a more favorable hydrogen bond (N—H···:N), the tetrahedral intermediate becomes locked into a configuration where reversion to the enzyme-substrate complex is no longer electronically allowed (the nitrogen electron pair is no longer antiperiplanar to the leaving oxygen of Ser-195). This implies that the leaving nitrogen via the N-inversion step acts as a switch controlling the mode of cleavage of the intermediate. The requirement for a conformational change involving His-57 fits well into

the first of six mechanistic schemes enumerated by Satterthwait and Jencks (22). According to this scheme, a rate-limiting conformational change of the enzyme during acylation had to be assumed in order to rationalize kinetic data. It is therefore quite reasonable to identify the assumed conformational change with the above mechanism proposed by Bizzozero, Zweifel, and Dutler (9, 10).

Experimental support for the above mechanistic interpretation comes from the work of Bizzozero and Zweifel (9) who have studied the behavior of N-acetyl-L-phenylalanyl-L-proline amide (31) and N-acetyl-L-phenylalanyl-sarcosine amide (32) toward enzymic hydrolysis with α-chymotrypsin. These two dipeptides were found to be good competitive inhibitors with a specific substrate (Ac-Phe-OCH_3 (33)) but no hydrolysis was observed. These two peptides thus form an enzyme-substrate complex and the reason for their non-reactivity has to be sought in the nature of the enzyme-substrate interactions occurring during the subsequent bond-change steps.



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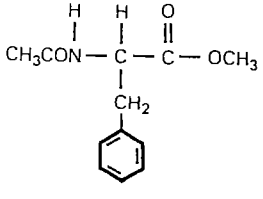

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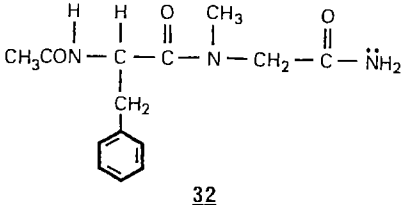
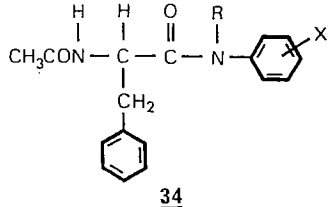


32

Application of the principle of stereoelectronic control predicts that the first tetrahedral intermediate must have conformation 21 rather than 23. As a result, the non-reactivity of the above two peptide substrates can be readily explained. In these two substrates, the amide nitrogen carries an extra alkyl substituent and molecular models show that this extra

alkyl substituent allows the formation of an enzyme-substrate complex (cf. 20, $\begin{smallmatrix} H & & R \\ | & & | \\ -N-R & = & -N-R \end{smallmatrix}$), but it does not permit the formation of a tetrahedral intermediate in the required conformation 21 ($\begin{smallmatrix} H & & R \\ | & & | \\ -N-R & = & -N-R \end{smallmatrix}$). Indeed, in 21 ($\begin{smallmatrix} H & & R \\ | & & | \\ -N-R & = & -N-R \end{smallmatrix}$), the extra N-alkyl substituent comes too close to the imidazole ring of His-57. Dipeptides 31 and 32 are therefore inactive because steric hindrance prevents formation of the tetrahedral intermediate. In normal substrates which have a hydrogen atom instead of an alkyl group pointing towards His-57, there is no steric hindrance and formation of the tetrahedral intermediate is possible (20 → 21). Again, it is worth pointing out that a conformation such as 22 ($\begin{smallmatrix} H & & R \\ | & & | \\ -N-R & = & -N-R \end{smallmatrix}$) (or 23), which is not sterically hindered, cannot be obtained directly from the enzyme-substrate complex unless the principle of stereoelectronic control is violated. The experimental results indicate that the violation of this principle is not allowed.

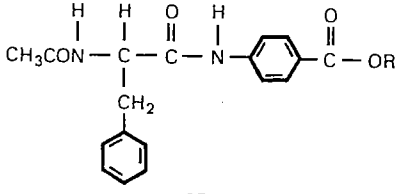
Petkov, Christova, and Stoineva (11) have reported a study on the hydrolysis of N-acetyl-L-phenylalanine anilide derivatives with α-chymotrypsin: N-methylated anilides 34 (R=CH_3) were found to be unreactive under the conditions used for the hydrolysis of N—H anilides 34 (R=H). These authors have explained their results in a manner analogous to that described above, i.e. no hydrolysis takes place because steric hindrance caused by the N-methyl group prevents the formation of a tetrahedral intermediate in the N-methyl anilide derivatives.



34

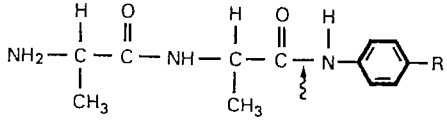
Petkov and Stoineva (12) have more recently reported that the relative rate of the α-chymotrypsin-catalyzed hydrolysis of p-alkoxycarbonyl anilide derivatives 35 of N-acetyl-L-phenylalanine is enhanced with an increase in the size of the R alkyl group of the leaving group. This rate enhancement specificity appears to be entropy controlled: the bulky alkyl groups increase both enthalpy and entropy of activation. These kinetic and thermodynamic data were interpreted in the following way: the bulky p-alkoxycarbonyl

aniline leaving group of the anilides does not fit sterically in the leaving-group-binding pocket of the enzyme. As a result of this lack of leaving-group-binding, rotation around the C—N bond is rendered easier in the transition state for the formation of the enzyme tetrahedral intermediate. It was concluded that this study provides further experimental evidence in favor of a conformational change at the nitrogen atom of the tetrahedral intermediate prior to cleavage as predicted by the principle of stereoelectronic control.



35

The anilide substrates L-Ala-L-Ala-pNA (36) and L-Ala-L-Pro-pNA (37) are hydrolyzed via a different rate-determining step by the serine protease, dipeptidyl-peptidase IV (12, 13). For 36, the rate-determining-step is the formation of the acyl-enzyme and for 37, it is the cleavage of this intermediate. This different behavior has been rationalized on the basis of arguments derived from the principle of stereoelectronic control in the hydrolytic process.



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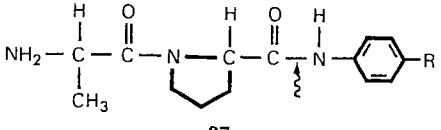
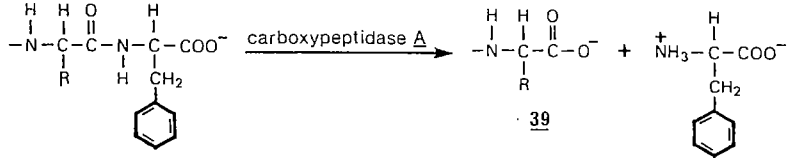


37

Carboxypeptidase A is a metalloenzyme (containing Zn^{+2}) which hydrolyzes the C-terminal peptide bond in polypeptide chains (1-4). The hydrolysis occurs most readily when the terminal amino acid residue has an aromatic (or a large aliphatic) R group (cf. 38 → 39+40).



38 39 40

The primary binding sites responsible for the catalytic activity of carboxypeptidase A are the following: (1) the metal ion (Zn^{+2}) coordinates the carbonyl oxygen of the amide function of the terminal amino acid. As a result, the carbonyl group reactivity is enhanced toward nucleophilic attack; (2) a hydrophobic pocket binds the aromatic side chain and the carboxylate ion of the terminal amino acid forms a salt linkage with the guanidinium cation of Arg-145. The hydrolytic process is illustrated in Fig. 3. The carboxylate ion of Glu-270 serves as a nucleophile which attacks the zinc-coordinated carbonyl group to form a tetrahedral intermediate (41 → 42). This intermediate then breaks down with concomitant proton transfer of the phenolic proton of Tyr-248 to the nitrogen atom yielding the acyl-enzyme, i.e. the mixed anhydride, and the terminal aromatic amino acid which is probably sterically prevented from leaving the active site until deacylation has occurred (23) (cf. 43). The acyl-enzyme is then hydrolyzed by reaction with water (via the formation of another tetrahedral intermediate) regenerating carboxypeptidase A (44) and yielding the hydrolyzed polypeptide 45 (24-28) and liberating the terminal aromatic amino acid 46.

Specific ester substrates are also hydrolyzed with carboxypeptidase A. For instance, Makinen, Fukuyama, and Kuo (27) have recently studied the enzymic hydrolysis of O-(trans-p-chlorocinnamoyl)-L-β-phenyllactate (CICPL) (47), and the spin labeled nitroxide ester substrate O-3-(2,2,5,5-tetramethylpyrrolinyl-1-oxyl)-propen-2-oyl-L-β-phenyllactate (TEPOPL) (48). They have shown that these reactions take place via the formation of a covalent intermediate (the mixed anhydride) which can be isolated under subzero temperature conditions. The hydrolysis of CICPL and TEPOPL catalyzed by carboxypeptidase A is consequently governed by the rate-limiting breaking of the acyl-enzyme.

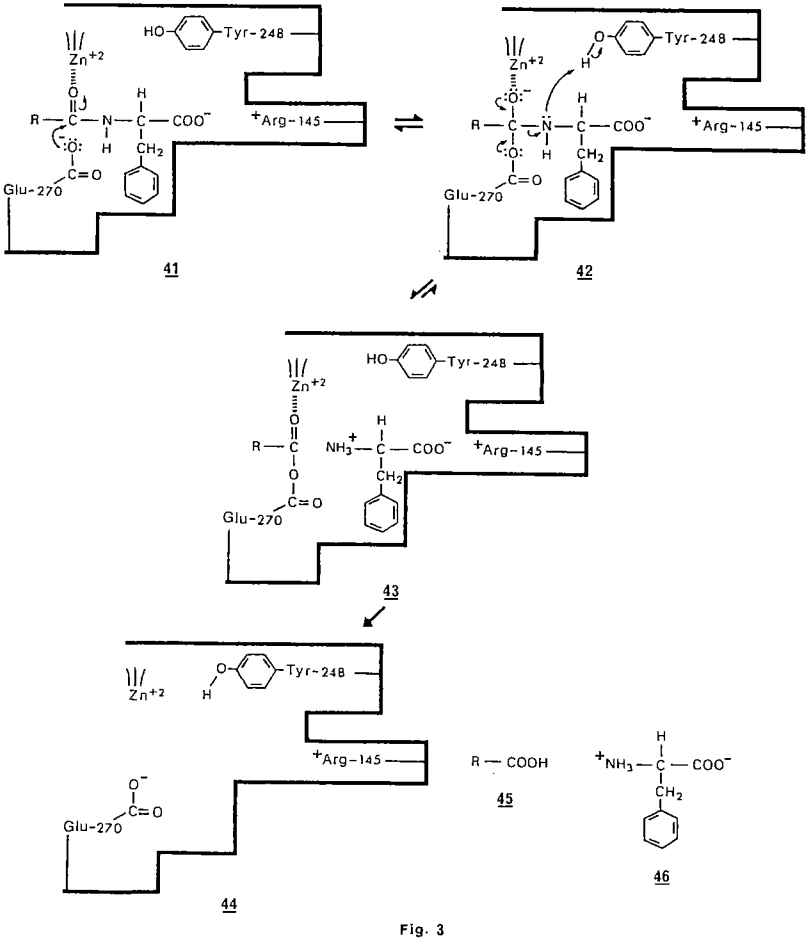
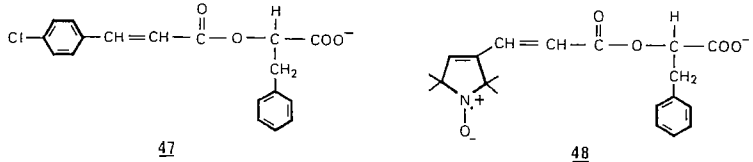


Fig. 3



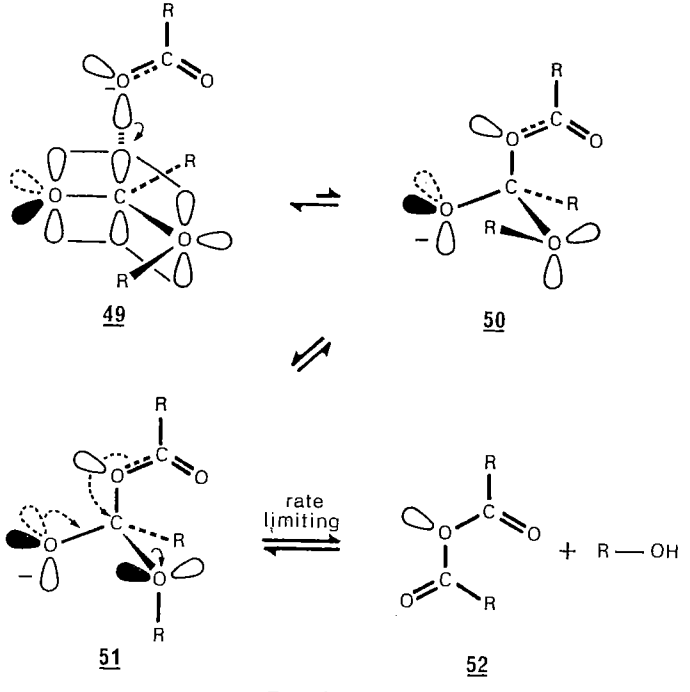
The same authors have also pointed out that the experimental results of others suggest that, with peptide substrates, the kinetics are different as the formation of the mixed anhydride intermediate is rate determining.

Kuo, Fukuyama, and Makinen (28) have further observed using molecular graphics techniques that the binding of the spin label TEPOPL (48) in the active site of carboxypeptidase A takes place with geometric strain and torsional distortion of the substrate. This is so because in the extended trans configuration, the bulky substituents of the pyrrolinyl ring of the spin label 48 are hindered by residues Ser-197, Tyr-198, Ser-199, and Ph-279. These amino acid residues have been defined as the sites of secondary substrate recognition. There is evidence of similar steric hindrance with oligopeptide substrates. The process of bond cleavage is thus dependent both upon interaction with the hydrophobic pocket and Arg-145 which fixes the substrate in the active site, and upon strain and distortion of the substrate by the site of secondary substrate recognition.

Interestingly, according to these authors, torsional distortion through interaction of the substrate with the sites of secondary substrate recognition is a requirement of the stereoelectronic effects which govern the cleavage of tetrahedral intermediates in the hydrolytic process. Inspection of molecular models shows that only one tetrahedral conformer is compatible with the structural constraints imposed by the active site. Indeed, substrate binding leads to the stereoelectronically allowed conformer 50 (Fig. 4) because of (a) coordination of the carbonyl group oxygen to the metal ion, (b) the binding (with Arg-145) of the COOH-terminus residue in the hydrophobic pocket and (c) the direction of approach of the nucleophilic γ-carboxylate group of Glu-270. (For the carboxylate ion preferred direction of approach towards the electrophile, see ref. 29).

Conformer 50 has the proper electron pair orientation to break down to give either the free ester substrate and the enzyme (cf. 49) or the mixed anhydride intermediate 52. The former process is however highly favored over the latter because (a) a carboxylate group is a much better leaving group than an alkoxy group and (b) the electron pair of an alkoxy group ($R\ddot{O}^{\curvearrowright}-$) is a better electron donor than that of an acyloxy group $\left(R-\overset{O}{\overset{\|}{C}}-\ddot{O}^{\curvearrowright}-\right)$. On the other hand, breakdown of conformer 51 obtained by rotation around the C—O alkyl bond in 50 can only give the mixed anhydride intermediate. Indeed, breakdown of conformer 51 to the free ester is not permitted electronically.

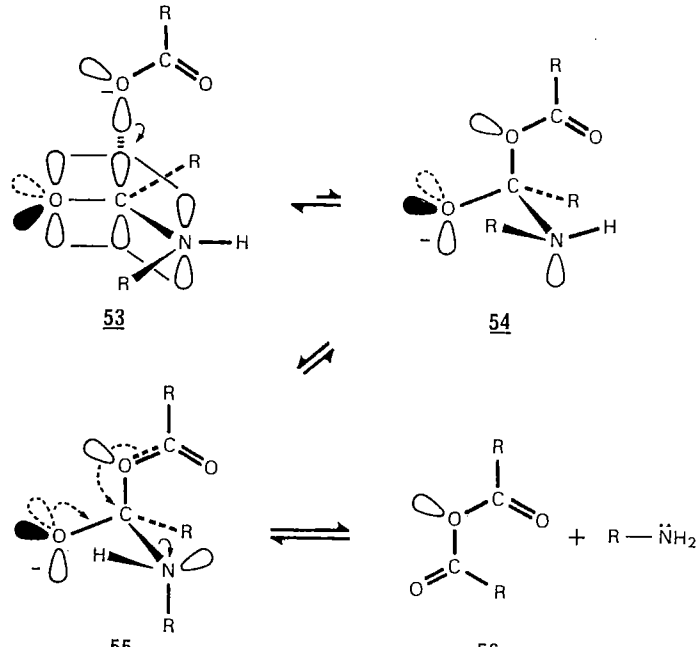
Thus, the collapse of the tetrahedral adduct to the mixed anhydride intermediate is determined purely by rotation around a single C – O bond of the tetrahedral species formed after substrate binding. The above authors have suggested that the torsional distortion of the substrate by the sites of secondary recognition provides the mechanical driving force that causes the required bond rotation to convert 50 into 51. This interpretation is supported by inspection of molecular models.



49 50 51 52

Fig. 4

The pathway by which the tetrahedral adduct formed in peptide hydrolysis is cleaved can be predicted by the same principle. Nucleophilic attack by the γ-carboxylate of Glu-270 on an oligopeptide substrate (53) in the active site of carboxypeptidase A must give the conformer 54 (Fig. 5). Conformer 54 has the proper electron pair orientation to break down to give either the peptide substrate and the enzyme (cf. 53) or the mixed anhydride intermediate 56. The former process is however highly favored over the latter because (a) a carboxylate group is a much better leaving group than an amino group



53 54 55 56

Fig. 5

and (b) the electron pair of an amino group is a better electron donor than that of an acyloxy group. As a result, the adduct 54 can be cleaved only non productively to reactants (→ 53). On the other hand, rotation around the C – N bond provides conformer 55 which can give the mixed anhydride 56 while the reversal to 53 is stereoelectronically forbidden. This rotation process is again favored by the secondary steric interactions. Thus, conformer 55 permits a productive cleavage of the C – N bond (→ 56) which takes place after or with concomitant proton transfer from Tyr-248 to the nitrogen atom (cf. 42 → 43).

It has been mentioned that the formation and the hydrolysis of the acyl-enzyme are respectively the rate-determining steps for oligopeptide and ester substrates. This different behavior can be readily explained by taking into account the different reactivity of the amide and the ester function. The amide function is electronically more stable than the ester function due to greater π-bonding. The amide carbonyl group is a relatively poor

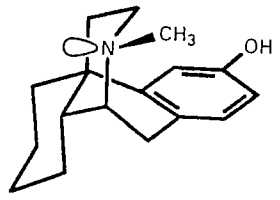
electrophile which is less vulnerable to nucleophilic attack than the ester carbonyl group. Consequently, the formation of a tetrahedral intermediate may require in the case of the amide an energy barrier sufficiently high to change the rate-limiting step of the process.

It can therefore be concluded that the sites of secondary substrate recognition of the enzyme which impose a strain on the substrate and cause a geometrical distortion of the tetrahedral intermediate, are an obligatory part of the catalytic action of carboxypeptidase A which takes place under stereoelectronically controlled conditions.

Structure-activity relationship

Belleau and collaborators (30-32) have recently pointed out that one aspect of conformation-activity relationships which has escaped attention concerns the importance of stereoelectronic effects. More specifically, they have proposed that stereoelectronic effects about the basic nitrogen of morphinans as opposed to stereoisomerism about chiral carbons play an important role at the analgesic receptor level. They have presented concrete evidence that the relative spatial orientation of the nitrogen lone pair in morphinans is of critical importance for productive interaction with the opiate receptors.

The opiate receptor displays absolute chiral specificity towards morphinans but relatively little towards structurally non-rigid narcotics of the piperidine and methadone classes. This is not surprising since flexible molecules are conformationally adaptable and thus more responsive to the geometric needs of the binding sites. The contrasting absolute chiral specificity of the receptor towards morphinans is very much like that of many enzymes towards their substrates. Interestingly, complete loss of receptor affinity was observed upon contraction of the six-membered piperidine ring found in morphinan (57) to a five-membered ring (58, D-normorphinan). Since it is known (30, 33) that in 58 the N-methyl group projects in a direction opposite to the phenyl ring while in 57, the same methyl group projects toward that ring, it was concluded that D-normorphinan (58) is inactive because the nitrogen lone pair responsible for the binding is not properly oriented. It is on this basis that Belleau and collaborators (30) suggested that the free N-lone pair of morphinans exerts an important stereoelectronic effect at the receptor level.



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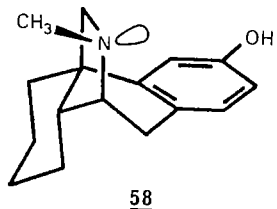

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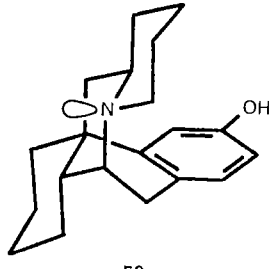

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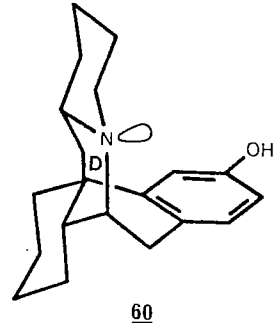

60

Further strong evidence that the lone pair orientation effect is indeed a major parameter controlling productive binding comes from the results obtained with the isomeric 16-α- and 16-β-butanomorphinans (31). The isomer 16-α-butanomorphinan is known to exist in conformation 60 where the piperidine ring D is locked in the boat conformation (34). Therefore, the nitrogen electron pair in 60 is rigidly oriented towards the phenyl ring (as in 58) and inability of this morphinan to bind on the opiate receptor should be achieved. Indeed, 60 is inactive. Contrary to this result, the 16-β-isomer displayed analgesic activity and it exists in conformation 59 where the nitrogen lone pair is in the opposite orientation (as in 57). Thus, the nitrogen lone pair orientation effect first noted with D-normorphinan 58 is of equal importance in genuine morphinans.

It was also suggested that the nitrogen lone pair is involved in a proton transfer when it interacts with the receptor. Thus, proton transfer would be required for a strong analgesics. This is in agreement with the effect of quaternization of the tertiary nitrogen (32) and deuterium isotope effect studies (31) which further support the conclusion that the N-lone pair of rigid morphinans should be properly oriented for facile proton transfer and induction of analgesia.

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