Industrial Chemistry Library, Volume 7

Advances in Organobromine Chemistry II

Jean-Roger Desmurs, Bernard Gérard
and Melvin J. Goldstein
(Editors)

Elsevier

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Industrial Chemistry Library

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Advances in Organobromine Chemistry II

Proceedings ORGABROM '93, Jerusalem,
June 28–July 2, 1993

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1995
ELSEVIER
Amsterdam — Lausanne — New York — Oxford — Shannon — Tokyo

ELSEVIER SCIENCE B.V.
Sara Burgerhartstraat 25
P.O. Box 211, 1000 AE Amsterdam, The Netherlands

ISBN: 0-444-82105-8

This book is printed on acid-free paper.

Printed in The Netherlands

PREFACE

This appearance of Volume 2 of "Advances in Organobromine Chemistry" means that the "series" now happily satisfies the minimal prerequisite for such a description. Spoken hitherto only as an act of faith by the publisher, by the organizers, by the sponsors, and by the participants, the "series" now begins in earnest.

Veteran readers might also recall Elsevier's 1988 publication of "Bromine Compounds; Chemistry and Applications", what was in effect, "Volume 0" of the subsequently designated series. That volume, like its successors, elaborated upon the proceedings of an international conference concerned with organobromine chemistry. The success of that first conference, like that of its succesors, depended critically on industrial financial sponsorship. From the original 1986 conference in Salford, principally sponsored by Associated Octel, to the 1989 conference in Thann, principally sponsored by the Rhône-Poulenc group, to the most recent 1993 conference in Jerusalem, principally sponsored by the Dead Sea Bromine group, the organobromine chemical industry continues to pay more than mere lip-service to the ideal of industrial-academic collaboration.

The number of published contributions continues also to grow with each succeeding volume : from fourteen in "Volume 0", then to twenty-seven, and now to thirty. Surely more important is the increasingly international character of the contributions : initially coming from only four countries, then from nine, and now from thirteen. Noteworthy too, if less easily quantifiable, is the increased sophistication and quality of the contributed manuscripts.

A common truism is to believe that modern methods of transportation and communication have transformed the world into a "global village". More accurately perhaps, the world is being transformed into a great number of different global villages, each one differing from the others in its focus on a particular common culture taken in the broadest sense of that word. These are not the villages defined by politicians or city planners. Many of them come instead, from the recognition that nationality plays an increasingly minor role in defining the cultural achievements of science and technology. In that context, appearance of this volume helps to establish Organobromine Chemistry as one such global village.

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ACKNOWLEDGEMENTS

We wish to thank the Dead Sea Bromine Group and The Hebrew University of Jerusalem for the Organization of Orgabrom'93. Particular thanks are due to Doctor Meir Englert, President of the organizing committee, Professor Yoel Sasson, President of the scientific committee, and to Mrs Rickie Raz for her valuable work in organizing the secretariat.

We wish to thank the Dead Sea Bromine Group also for the material support that made the Orgabrom'93 congress possible.

Furthermore, we are very grateful to the ALBEMARLE Corporation for the financial contribution which permitted the publication of this book.

Finally, we wish to thank the authors for their contribution and help in the publication of this book.

Jean-Roger DESMURS Bernard GERARD Melvin J. GOLDSTEIN

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CONTENTS

PREPARATION OF ORGANOBROMINATED COMPOUNDS
REACTION MECHANISMS

USE OF ORGANOBROMINATED COMPOUNDS
SYNTHESIS

USE OF ORGANOBROMINATED COMPOUNDS
REACTION MECHANISM

INDUSTRIAL ASPECTS

ENVIRONMENT

TOXICOLOGY

ANALYSIS

INTRODUCTION

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At the outset of 1994 there is evidently more public (and perhaps professional) interest in the destruction of organic halogen compounds (ref. 1) than in their creation.

Of major concern are the health and environmental impacts of the abundant chlorinated and brominated hydrocarbons (ref. 2). These materials have numerous industrial applications as pesticides, solvents, propellants, refrigerants, plastics, fire retardants and extinguishers, disinfectants for drinking water, pharmaceuticals and electronic chemicals. Many chemical manufacturers utilize chlorinated and brominated organics as intermediates. It is estimated, for instance, that almost 85 % of the pharmaceuticals produced in the world require chlorine at some stage of synthesis.

Evidence that many of these compounds can have adverse effects on the immune, endocrine and nervous systems and that some are carcinogenic has grown during the last decade. The role of chlorofluorocarbons (CFCs) and of methyl bromide in the ozone layer depletion is well established (ref. 3).It is therefore not surprising that many halogenated derivatives are cast as environmental and health villains by various concerned groups who call for total phase out of chlorine and chlorinated hydrocarbons.

Several of the commercially available 16,000 chlorinated and brominated compounds have already been regulated or banned, CFCs, DDT and chlorinated biphenyls are typical examples. Many others are being phased out according to the Montreal Protocol on Substances that Deplete the Ozone Layer. This includes chlorinated solvents, methyl bromide and halons (e.g. CF_3Br). The milder ozone destroyers, hydrochlorofluorocarbons (HCFCs) will also, eventually, be phased out.

Organohalogen compounds are of serious concern also as contaminants. The most feared material in this category is dioxin (2,3,7,8-tetrachlorodibenzo-para-dioxin, TCDD) that has already caused several catastrophes and has even been detected in effluent and sludge from paper mills that use chlorine bleach and also in

the effluents of municipal and hazardous-waste incinerators (ref. 4).There are also some evidences that chlorine based polymers (PVC), or plastics containing brominated fire retardants, release dioxins upon burning. Concern over the formation of trihalomethanes in drinking water is also thoroughly documented (ref. 5).

Even so, one cannot overlook the immense advancement in development of novel synthetic halogenation methods concomitant with an extensive progress in comprehension of halogenation mechanisms that has taken place during the last decade. Organohalogen compounds still find interesting new uses and applications. The astonishing observation that the introduction of chlorine (and bromine!) substituents enhance the sweetness of sugars by two orders of magnitude (ref. 6) has led to the development of the trichlorinated sweetner sucralose (refs. 7,8). Halogenated carbohydrates are finding other new uses such as antibiotics, anticarcinogenics (ref. 9) and male antifertility agents (ref. 10). Organo bromine compounds are practiced in numerous applications as intermediates in the pharmaceutical industry (ref. 11). Aromatic iodine derivatives are effectual as contrast media for diagnostic imaging by x-ray or magnetic resonance imaging (ref. 12). New halogenation methods, such as the homolytic bromination in supercritical carbon dioxide (ref. 13) and aromatic chlorinations in liquid HCl (ref. 14) are being developed. Large numbers of halogenated marine natural products have been isolated and identified. The mechanism of their biosyntheses has been elucidated and the enzymes involved (haloperoxidases) have been isolated and put to novel synthetic use (e.g. the enzymatic labeling of proteins with ^{77}Br[15]). The quantities of the naturally produced halomethanes are enormous, it is estimated that 300,000 tons of methyl bromide and 5 million tons of methyl chloride are produced annually by marine and terrestrial biomass (refs. 16,17).

Another exciting developing field is in material science. Chlorination and bromination of fullerenes (refs. 18,19) and solid state bromination of poly-acetylenes (refs. 20,21) and of polybutadienes (ref. 22) are typical examples.

This symposium addressed several important issues in bromine chemistry. A major part has been devoted to stereochemistry and mechanism of electrophilic bromination of olefins. Other topics included new selective methods of bromination and oxybromination, brominations in presence of solid supports and catalysts, organobromine compounds as synthons, recent developments in brominated fire retardants and toxicological and environmental aspects of brominated compounds.

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REGIOSELECTIVE BROMINATION OF PHENOLS

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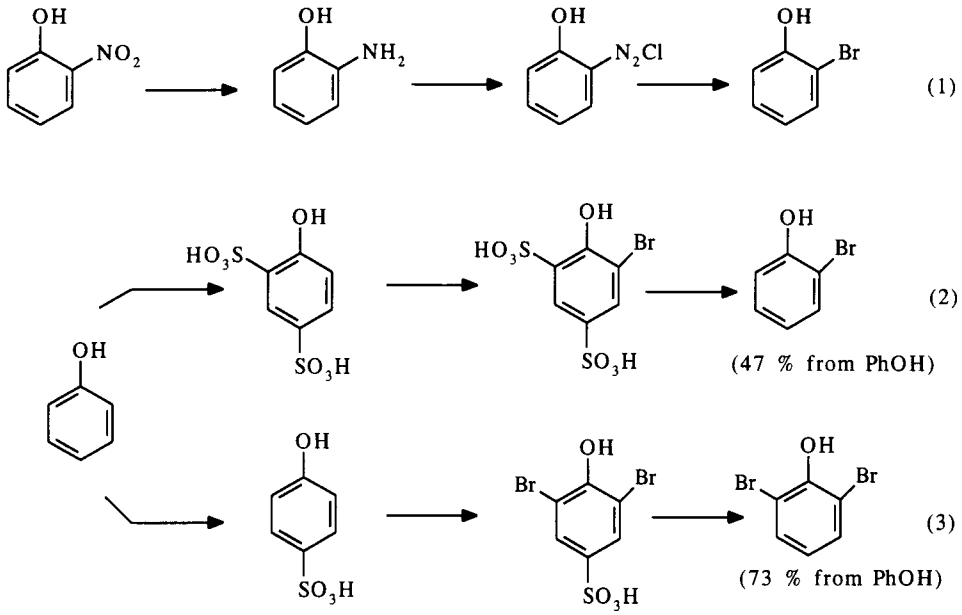
ABSTRACT

Regioselective bromination of phenols gave 2-bromo-, 4-bromo-, 2,6-dibromo-, 2,4-dibromo, 2-bromo-6-substituted, 4-bromo-2-substituted and 2,4-dibromo-6-substituted phenols, respectively. Especially, 2-bromo-, 2,6-dibromo- and 2-bromo-6-substituted phenols which were prepared *via* long steps, were obtained in NBS-amine (primary and secondary) system in high yields under ordinary conditions. The scope and their mechanisms were discussed.

INTRODUCTION

Various bromophenols are useful precursors for medicinal drugs, agricultural chemicals, dyes, and flame retardants. It is difficult to synthesize directly *ortho*-bromophenols by use of bromine with which bromination afford *para*-substitution predominantly (ref. 1). Thus desired *ortho*-bromophenols were generally prepared *via* tedious steps as shown in Scheme 1 (refs. 2,3).



Scheme 1. Different methods of synthesis of *o*-bromophenols

Several methods for direct *ortho*-bromination and *ortho*-dibromination of phenols have been reported (refs. 4,5). Pearson et al. (ref. 6) found that treatment of phenols with bromine in the presence of a large excess of *t*-butylamine at - 70°C gave 2-bromo- or 2,6-dibromophenols in good yields. Recently, Schmitz et al. (ref. 7) showed that the reaction between phenol and *N,N*-dibromomethylamine efficiently affords 2,6-dibromophenol.

However, the former reaction requires very low temperatures and very dilute conditions and the latter uses an unstable and explosive brominating reagent.

In this article we describe selective bromination of various phenols under mild conditions and discuss their reaction mechanisms.

REGIOSELECTIVE BROMINATION OF PHENOL

Solvent effects

Calo et al. (ref. 5) studied solvent effects on selective bromination of phenol with NBS and found the selectivity of bromination depended on the polarity of the solvents. But thereafter no investigation concerning the solvent effects was reported. We report the effects systematically.

The results of the bromination of phenol with NBS compared with bromine in various solvents are shown (Fig. 1). NBS was not added as the solution in solvent but solid powder.

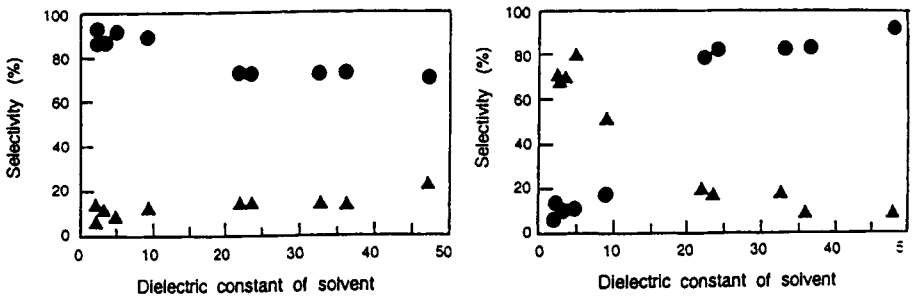


Fig. 1. Plots of dielectric constant *vs* selectivity of bromination of phenol with Br_2 (left) and NBS (solid powder) (right). *ortho*-Bromophenol (▲), *para*-Bromophenol (●).

Although bromine leads to exclusive *para*-bromide in every solvent, it was recognized NBS in weakly polar solvents (CCl_4, C_6H_6, C_6H_5Br, $CHCl_3$, CH_2Cl_2) gave *ortho*-bromide and NBS in polar solvents (PrOH, EtOH, MeOH, DMF, DMSO) gave *para*-bromide.

Dichloromethane (DC : 9.10) is one of the most suitable solvent for *ortho*-bromination because of its easy handling, and high solvent power for NBS.

Effects of Brominating Reagents

In Table 1 was shown the results of bromination of phenol with bromine, NBS, and *N*-bromodibutylamine (NBB) (ref. 8) in dichloromethane.

Table 1. Bromination of Phenol with Bromine, NBS, and *N*-Bromodibutylamine (NBB)[a)]

		Product yield (%) [b)]					Recovery (%)
Reagent	Reagent / PhOH	2,6-dibromo-phenol	2,4,6-tribromo-phenol	2-bromo-phenol	2,4-dibromo-phenol	4-bromo-phenol	
Br_2	1.0	-	-	10.7	1.0	85.7	2.6
Br_2	2.0	-	0.8	1.0	95.1	3.0	-
NBS	1.0	1.0	1.5	74.5	1.4	20.4	2.5
NBS	2.0	11.0	35.2	21.9	17.2	14.6	1.2
NBB	1.0	28.8	0.7	30.8	2.1	1.9	35.7
NBB	2.0	81.7	5.8	3.8	2.7	0.7	5.3

a) Reactions were carried out at room temperature.
b) Yields of the products were determined by GC.

Monobromination with bromine leads to exclusive 4-bromophenol, and dibromination with the same reagent gave predominant 2,4-dibromophenol. In the case of monobromination with NBS, the main product was 2-bromophenol, but no selectivity appeared in the bromination using two molar amounts of NBS.

As described above, it was shown that *N,N*-dibromomethylamine was effective for *ortho*-dibromination of phenol (ref. 7). We also carried out a bromination using NBB as *N*-bromoamine analogue. One molar amount of NBB did not give 2-bromophenol selectively, but gave a mixture of *ortho*-monobromophenol and 2,6-dibromophenol, and a considerable amount of phenol was recovered. On the other hand, 2,6-dibromophenol was obtained in an 81.7 % yield when two molar amounts of NBB were used. These results suggested that *N*-bromoamines were the best reagents for *ortho*-bromination of phenol. However *N*-bromoamines were very unstable and decomposed explosively in less than a day at room temperature.

Amines Catalyzed *ortho*-Bromination (ref. 9)

We considered *N*-bromoamines which generated *in situ* from the reaction of NBS and various amines, should promote the *ortho*-dibromination of phenol. The results of the bromination with NBS in the presence of amines are summarized in Table 2.

Table 2. Dibromination of Phenol with NBS in the Presence of Primary, Secondary, and Tertiary Amines[a)]

Amine[b)]	Product yield (%) [c)]					Recovery (%)
	2,6-dibromo-phenol	2,4,6-tribromo-phenol	2-bromo-phenol	2,4-dibromo-phenol	4-bromo-phenol	
-	11.0	35.2	21.9	17.2	14.6	1.2
i-$PrNH_2$	69.3	10.5	14.4	0.7	1.4	3.8
n-$BuNH_2$	78.9	11.6	4.0	1.1	0.6	3.8
i-$BuNH_2$	65.4	16.0	11.2	0.7	0.5	6.2
$(n\text{-}Pr)_2NH$	72.1	11.7	9.0	1.2	0.7	5.2
$(i\text{-}Pr)_2NH$	81.8	10.7	3.2	1.4	0.8	2.2
$(n\text{-}Bu)_2NH$	79.3	7.9	6.8	1.3	0.7	3.9
Et_3N	13.6	34.8	16.1	17.4	9.6	8.5
$(n\text{-}Pr)_3N$	10.6	38.0	13.3	17.8	11.2	9.0
$(n\text{-}C_5H_{11})_3N$	18.1	34.2	11.4	17.5	13.5	5.4

a) Reactions were carried out at room temperature.
b) Molar ratio of PhOH : NBS : amine = 1 : 2 : 2.
c) Yields of the products were determined by GC.

Addition of every primary amine was effective for obtaining the *ortho*-dibromide selectively. In the absence of amines, the yield of 2,6-dibromophenol was much lower than that of 2,4,6-tribromophenol. The selective *ortho*-dibromination of phenols was also observed when secondary amines were added.

Particularly, diisopropylamine and dibutylamine showed high *ortho*-selectivity. Addition of tertiary amines, such as triethylamine, tripropylamine, and tripentylamine was ineffective in the *ortho*-selectivity. In this system *N*-bromoamine never generates.

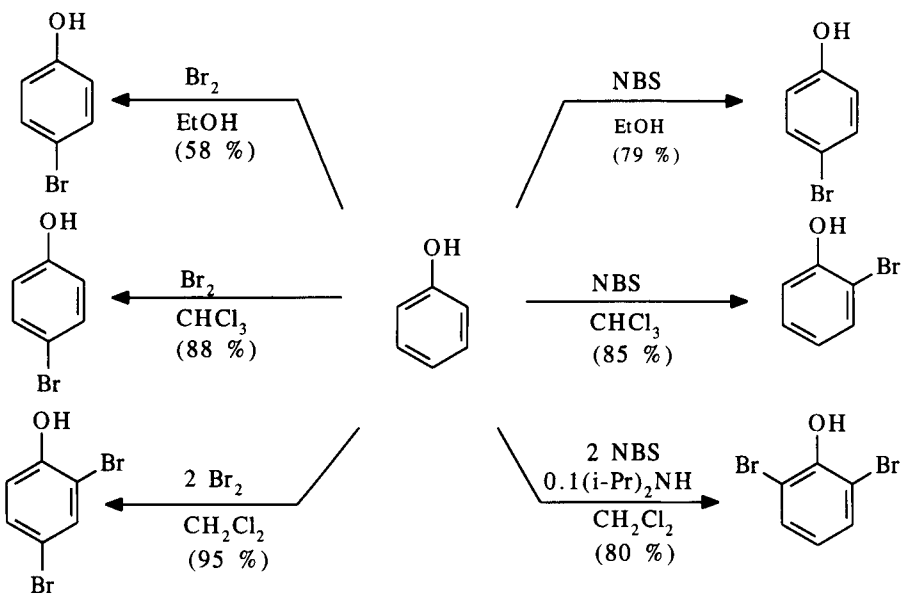
Table 3 shows the relation between the yields of the products and the amounts of added diisopropylamine which showed the highest *ortho*-selectivity.

Table 3. Dibromination of Phenol with NBS in the Presence of Various Amounts of $(i\text{-Pr})_2NH$[a)]

run	Molar ratio NBS/amine/ PhOH	Product yield (%) [b)] 2,6-dibromo- phenol	2,4,6-tribromo- phenol	2-bromo- phenol	2,4-dibromo- phenol	4-bromo- phenol	Recovery (%)
1	2.0/0.1/1.0	79.4	12.4	3.6	-	0.2	4.3
2	2.0/0.5/1.0	80.8	8.0	8.3	-	0.7	2.1
3	2.0/1.0/1.0	80.5	11.1	4.7	0.3	0.3	3.1
4	2.0/2.0/1.0	81.8	10.7	3.2	1.4	0.8	2.2
5	2.0/4.0/1.0	79.5	9.2	5.6	0.6	1.2	3.9
6	1.0/0.1/1.0	33.1	2.0	26.7	0.2	0.3	37.7
7	1.0/---/1.0	1.0	1.5	74.5	1.4	20.4	2.5

a) Reactions were carried out at room temperature.
b) Yields of the products were determinated by GC.

The distribution of the products was only slightly influenced by the added amount of the amine in the bromination. Even a 0.1 molar amount of diisopropylamine was sufficiently effective. From these results, it was concluded that the amine worked catalytically in the selective *ortho*-bromination of phenol. Regioselective bromination of phenol was summarized in Scheme 2.



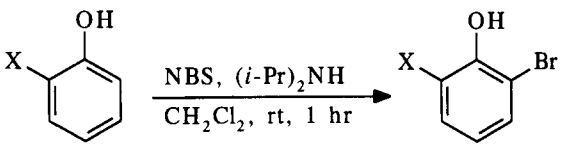
Scheme 2. Summarize of bromination of phenol

REGIOSELECTIVE BROMINATION OF 2-SUBSTITUTED PHENOLS

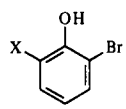
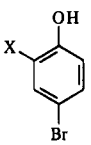
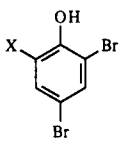
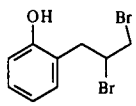
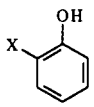
Ortho-Bromination

Our method, NBS-amine system, is applied to *ortho*-bromination of 2-substituted phenols (e.g. 2-allylphenol, *o*-cresol, 2-bromophenol, and 2-chlorophenol) (Table 4).

Table 4. Bromination of 2-Substituted Phenols with NBS, Br_2, and BTMA.Br_3[a)]



(4)

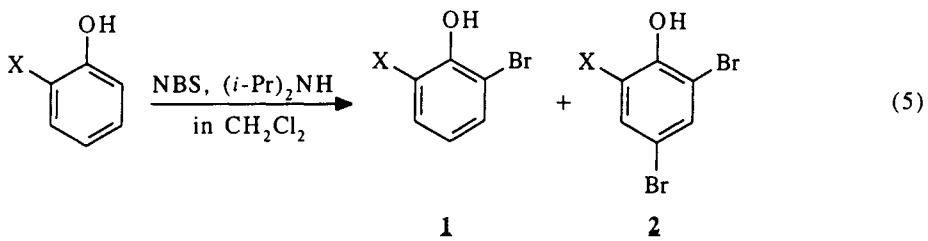
Substrate X	Reagent[b)]	$(iPr)_2NH$ /PhOH	Product yield (%)[c)]				Recovery (%)
							
Br	Br_2	-	13.7	81.3	2.4		2.6
Br	NBS	-	18.4	22.5	29.4		29.6
Br	NBS	0.1	82.0	--	5.7		12.3
Cl	Br_2	-	7.1	77.1	1.4		14.3
Cl	NBS	-	27.1	17.7	24.8		30.4
Cl	NBS	0.1	84.2	-	8.1		8.4
Allyl	BTMA.Br_3	-	-	6.5	-	83.0	6.2[d)]
Allyl	NBS	-	79.5	3.2	6.5	-	10.8
Allyl	NBS	0.1	94.0	-	1.9	-	4.1
Me	Br_2	-	2.7	94.0	0.3		2.9
Me	NBS	-	75.4	21.1	1.5		2.0
Me	NBS	0.1	96.5	0.4	1.5		1.5

a) Reactions were carried out at room temperature.
b) Molar ratio of reagent : PhOH = 1 : 1.
c) Yields of the products were determined by GC.
d) 2-Bromomethyl-2,3-dihydrobenzofuran was obtained in 4,3 %.

The results were compared with the bromination with bromine. It was apparent that bromine gave *para*-bromides exclusively except 2-allylphenol. As the reaction of 2-allylphenol with bromine gave the mixture of many products (bromine adduct as main product, some ring bromides as by-products, etc.), 2-allylphenol was treated with benzyltrimethylammonium tribromide (BTMA Br_3) which was already developed as mild and easy bromine (ref. 10).

Consequently the bromine adduct was obtained in high yield (83 %). Using NBS and a catalytic amount of the amine, the ratio of the *ortho*-brominated phenols was remarkably raised. 2-Allylphenol and *o*-cresol were considerably *ortho*-brominated by NBS even without the amine. In NBS-amine system dibromides as by-products were obtained slightly and any *para*-bromide and bromine adduct in the case of 2-allylphenol were not detected.

In Figure 2 was shown the correlation of the reaction temperature and selectivity of bromination of 2-substituted phenols. (eqn. 5)



(5)

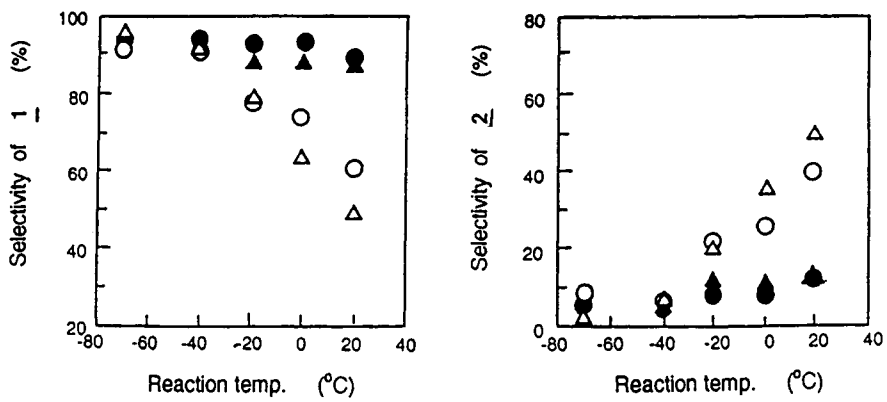


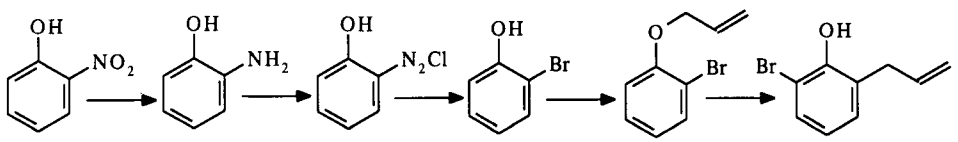
Fig. 2 Selectivity of *ortho*-bromide (left) and dibromide (right) depending on reaction temperature in the bromination of 2-substituted phenols with NBS (solid powder) and $(i\text{-Pr})_2NH$. 2-allylphenol (●), *o*-cresol (▲), 2-bromophenol (Δ), and 2-chlorophenol (O).

In this experiment NBS was added as solid powder. Every substrates were converted into *ortho*-bromides in high yield at low temperature, but in the case of phenols having electron-accepting groups, yield of *ortho*-bromides lowered and those of by-products (dibromides) increased at high temperature (> 20°C). Thus, 2,6-dihalophenols which were produced once, easily formed phenoxides ion because of the interaction with free diisopropylamine or NHS (succinimide) and were attacked at *para*-position by the excess brominating reagent at room temperature and finally resulted in 2,4,6-trihalophenols.

Regioselective Bromination of 2-Allylphenol

It is generally supported that the bromination with NBS proceeded by a radical (ref. 11) or an ionic mechanism *via* bromine molecule. For instance, the former was suggested in benzylic and allylic bromination with NBS for Whol-Ziegler reaction (ref. 12). Calò et al. (ref. 5) accounted NBS brominated phenol by the latter mechanism.

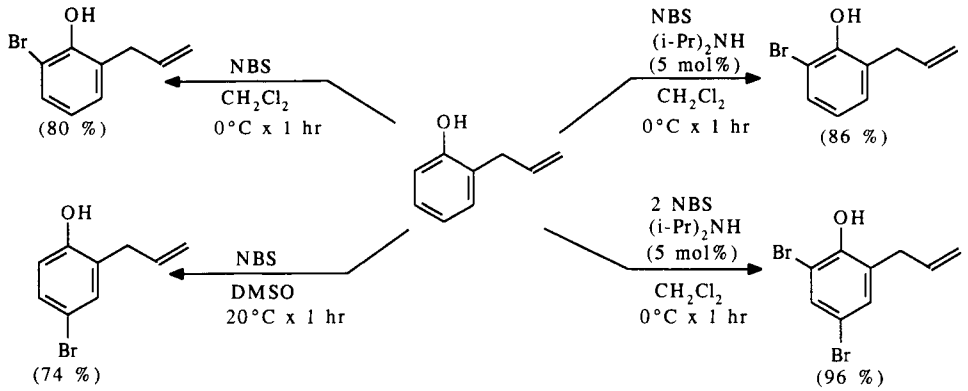
2-Allyl-6-bromophenol, the precursor of prostacyclin analogues, is usually prepared by the way as shown in Scheme 3 (ref. 13).



Scheme 3. Synthesis of 2-allyl-6-bromophenol

In the above section we describe the convenient preparation of 2-allyl-6-bromophenol without any bromine adduct. It seems that these results are not able to be explained by the mechanisms *via* bromine molecule, which are described later.

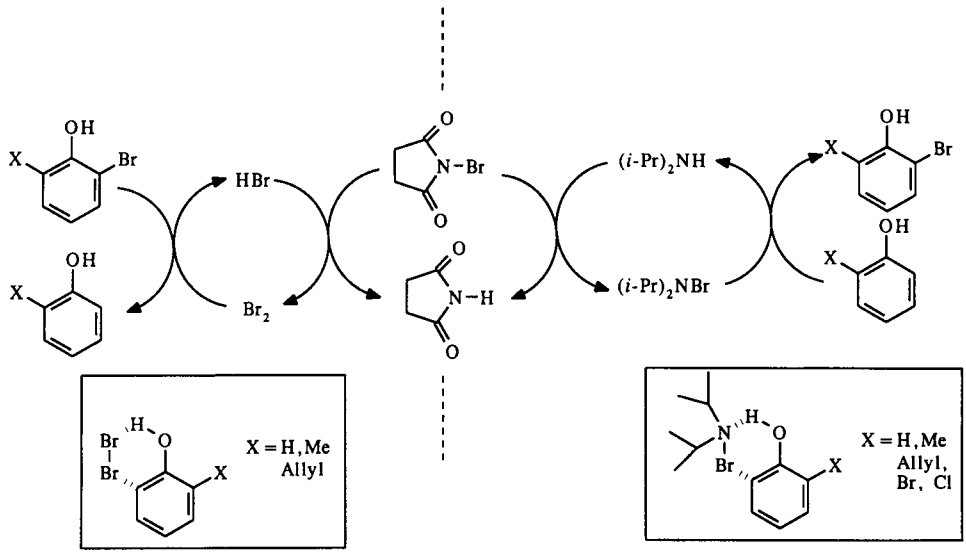
Useful methods for the preparation of various bromosubstituted 2-allylphenols were proposed in Scheme 4.



Scheme 4. Preparation of various bromosubstituted 2-allylphenols

MECHANISTIC CONSIDERATION

The mechanism of the *ortho*-dibromination of phenol with NBS in the presence of amines is considered as follows. The hydrogen bonding between phenol and *N*-bromoamine which are generated from the reaction of NBS and amines (ref. 14), is the driving force, and causes the bromination at one *ortho*-position of phenol and regeneration of the amines. A catalytic amount of the amines is enough because of the regeneration of the amines. The repetition of the above process causes one more substitution at the other *ortho*-position of 2-bromophenol. In the cases of 2-substituted phenols the *ortho*-bromination can occur only once (Scheme 5).



Scheme 5. Mechanism of *o*-bromination with NBS in the presence of amines (right) and in the absence of amine (left).

Because the tertiary amines cannot be brominated by NBS, they do not influence the *ortho*-bromination of phenols. Though the hydrogen bonding between the phenolic OH and NBS will be formed, the bonding is inferred to be weaker than that between the OH and the *N*-bromoamines. The nucleophilicity (or basicity) of the nitrogen atom of *N*-bromoamines is stronger than that of NBS. This is why traces of *N*-bromoamines can react with phenols continuously.

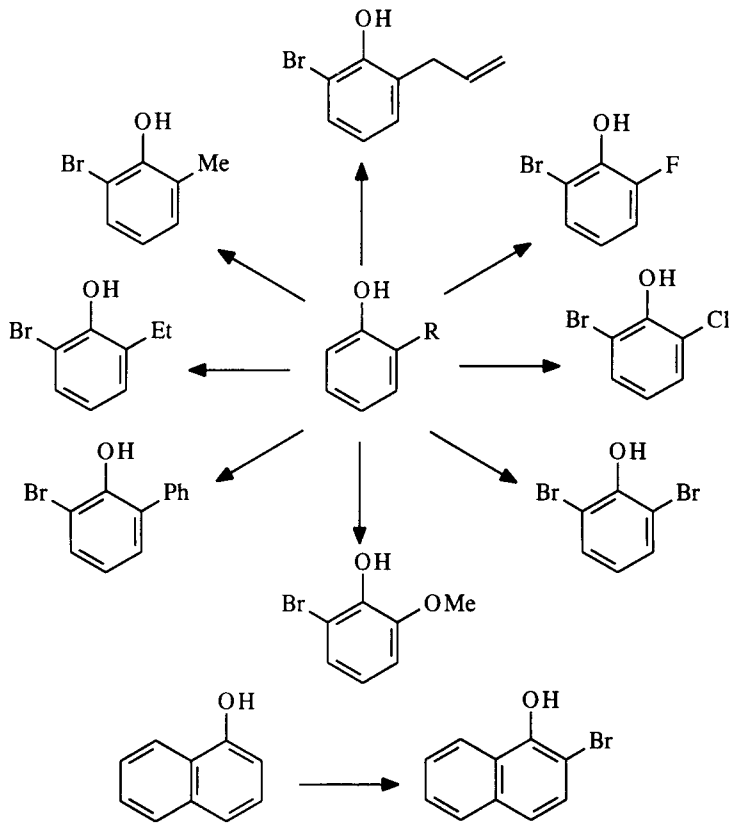
Mechanism of *ortho*-bromination of 2-substituted phenols (substituents : H, Me, Allyl) with NBS in the absence of amine was shown in Scheme 5 (left). It was explained the hydrogen bonding between phenolic OH and NBS was weak in NBS-amine system. The hydrogen bonding between OH and NBS which may be formed in only NBS system, is deduced not to contribute to *ortho*-bromination (ref. 15). As described by Calo (ref. 5), hydrogen bonding between these phenols and catalytic amount of bromine which is contained in NBS, is formed and then *ortho*-bromination proceeds. Hydrogen bromide generated at this time is scavenged by NBS and bromine was regenerated.

Hydrogen bonding between Br_2 and 2-substituted phenols having electron-donating group is strong enough to *ortho*-brominate these phenols. Therefore, *ortho*-bromination of phenol, o-cresol and 2-allylphenol was promoted by only NBS without amines.

Faster *ortho*-bromination than bromine addition is the reason why bromine adduct was not obtained in the bromination of 2-allylphenol with NBS (ref. 15).

CONCLUSION

Because of its mild reaction conditions, simple experimental operations, and generally excellent yields of *ortho*-bromophenols, our method is practical for a wide variety of bromination of phenols (Scheme 6) and expected for industrial preparation of fine chemicals.



Scheme 6. *ortho*-Bromination of phenols

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BROMINATION OF AROMATIC COMPOUNDS WITH ALUMINA-SUPPORTED COPPER(II) BROMIDES

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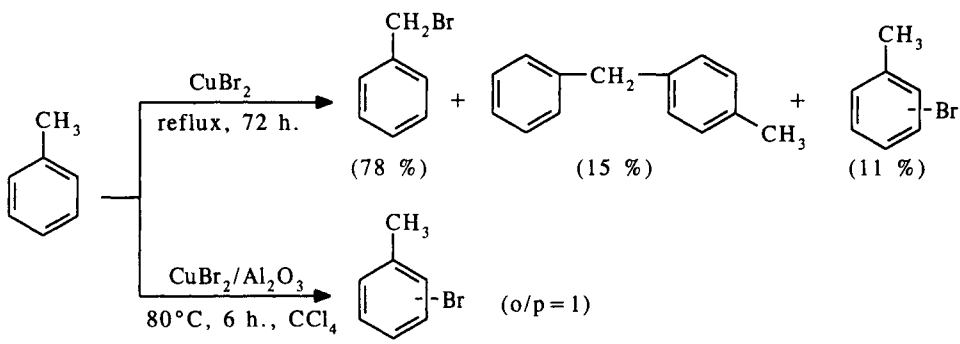
Copper(II) halides have been used as halogenating agents in homogeneous conditions for compounds containing active hydrogen atoms (refs 1,2), and in heterogeneous in nonpolar solvents for aromatic hydrocarbons (refs 3,4). For example, anthracene and pyrene react with copper(II) chloride and bromide in heterogeneous conditions to give excellent yield of 9-haloanthracenes and 1-halopyrenes (ref. 5). However, the process is not generally applicable for halogenation of all aromatic compounds. Aromatic hydrocarbons with ionization potentials higher than approximately 7.55 eV were found to be entirely unreactive toward chlorination with copper (II) chloride (ref. 6). In reactions of alkylbenzenes with copper(II) halides, side-chain-halogenation and polymerization in addition to nuclear-halogenation occur (ref. 7). 1-Alkoxynaphtalenes react with copper(II) bromide in heterogeneous conditions to give a mixture of 4-bromo-1-alkoxynaphtalenes and 4,4'-dialkoxy-1, 1'-binaphtyls. Previously, we reported that copper(II) halides can be activated remarkably by supporting onto neutral alumina, and halogenated phenylacetylene selectively to give 1-halo-2-phenylacetylene or 1,1,2-trihalo-2-phenyl-ethylene in non polar solvents under mild conditions (ref. 8). Here, we report that a facile method for selective nuclear bromination of aromatic compounds (polymethylbenzenes, polycyclic aromatic hydrocarbons, alkoxy-benzenes, alkoxynaphtalenes and alkoxythionaphtalenes) by use of alumina-supported copper(II) bromide.

BROMINATION OF AROMATIC HYDROCARBONS

Bromination of Polymethylbenzenes.

Halogenation of alkylbenzenes with metal halides gave mixtures of nuclear-halogenated compounds and side-chain-halogenated compounds (ref. 7). The halogenation of polymethylbenzenes with alumina-supported copper(II) halides in nonpolar solvents in which copper(II) halides were not soluble, occurred as a heterogeneous reaction on the surface and gave only nuclear-halogenated compounds in high yields; no side-chain-halogenated compounds were obtained (ref. 9). The reaction of copper(II) bromide with mesitylene in carbon tetrachloride at reflux yielded no detectable products after 5 h. In contrast, in a similar reaction using alumina-supported copper(II) bromide, bromomesitylene in 97 % yield from a reaction run at 50°C for 1 h. and dibromomesitylene in 99 % yield from the reaction run at 80°C for 5 h. were obtained. The results of bromination of polymethylbenzenes are summarized in Table 1. Reactivity of the polymethylbenzenes toward copper(II) bromide increased with increasing number of methyl groups, as follows : mesitylene > p-xylene > toluene.

For instance, bromination of toluene in carbon tetrachloride did not proceed at reflux, even though pentamethylbenzene was brominated at 30°C to give bromopentamethylbenzene quantitatively. Toluene and copper(II) bromide reacted at reflux for 72 h. to give benzyl bromide as the main product. In a similar reaction with alumina-supported copper(II) bromide, bromotoluene (o/p=1) was obtained in good yield and no side-chain-brominated compounds were detected.



Scheme 1. Bromination of toluene with $CuBr_2$

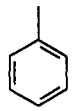
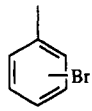
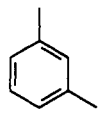
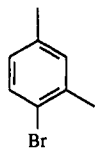
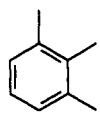
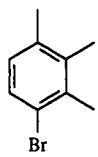
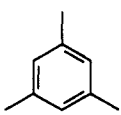
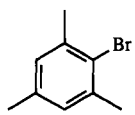
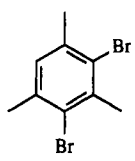
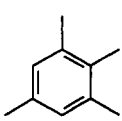
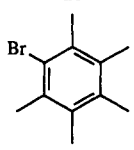
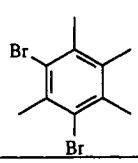
The reaction of alkylbenzenes with copper(II) bromide is critically influenced by the presence of water in small quantities (ref. 10). With toluene, nuclear bromination predominates in a rigorously anhydrous system. When small amounts

of water are added, phenyl(p-tolyl)methane is the main product, in addition to benzyl bromide. In contrast, in a reaction with alumina-supported copper(II) bromide in the presence of water in small quantities, only nuclear bromination occurred and no products resulting from side-chain-bromination were formed. It seems that alumina not only activates copper(II) halides but also acts as a dehydrating agent in this system. Copper(II) chloride was less reactive than copper(II) bromide toward the polymethylbenzenes. The chlorination of xylene did not occur under the same conditions, even though the bromination proceeded at 80°C in carbon tetrachloride.

Bromination of Polycyclic Aromatic Hydrocarbons

Aromatic hydrocarbons with ionization potential (IP) higher than approximately 7.55 eV are entirely unreactive toward chlorination with copper(II) chloride (ref. 6). Even under reflux with copper(II) chloride in high-boiling solvents, e.g., nitro-benzene and chlorobenzene, chlorination of naphtalene (IP=8.10) (ref. 11) or phenanthrene (IP =8.03) (ref. 11) was not successful. When alumina-supported copper(II) halides was used as halogenating agents, aromatic hydrocarbons with ionization potential higher than 7.55 eV were easily halogenated to give mono- or dihalogenated products (ref. 12). For example, while reaction of naphtalene with copper(II) chloride in refluxing chlorobenzene produced negligible yields of chlorinated products, similar reaction with alumina-supported copper(II) chloride produced monochlorinated compounds in high yields. Copper(II) bromide was more reactive than copper(II) chloride toward the aromatic hydrocarbons. Bromination of aromatic hydrocarbons proceeded in carbon tetrachloride to give the corresponding bromo compounds with high selectivity. Mono- or dibromo compounds were selectively obtained in high yield depending upon the reaction conditions. The reaction of naphtalene with copper(II) bromide in carbon tetrachloride at 80°C for 15 h. produced 10 % yield of 1-bromonaphtalene. In contrast, in a similar reaction using alumina-supported copper(II) bromide, 1-bromonaphtalene in 98 % yield from a reaction run at 80°C for 2 h. and 1,4-dibromonaphtalene in 92 % yield from the reaction run in chlorobenzene at 130°C for 1 h. were obtained.

Table 1. Bromination of Polymethylbenzenes with $CuBr_2/Al_2O_3$[a)]

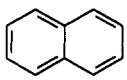
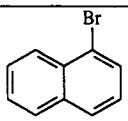
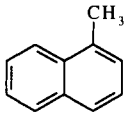
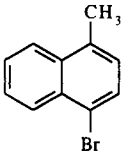
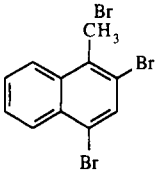
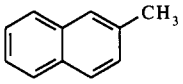
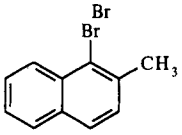
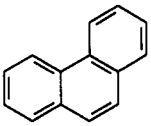
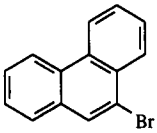
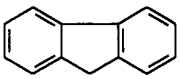
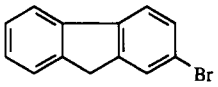
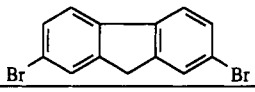
Polymethylbenzene	°C/h	Product	Yield (%)[b)]
	80/6		85[c)]
	80/2		98(85)
	80/1		97(87)
	50/1		97(86)
	80/5		99(97)
	50/1		92(90)
	80/5		(99)

a) All the reactions carried out in carbon tetrachloride.
The molar ratio of $CuBr_2$/polymethylbenzene was 5.

b) Determined by GLC; figures in parenthese show the yield of isolated product

c) o/p = 1

Table 2. Bromination of Polycyclic Aromatic Hydrocarbons with $CuBr_2/Al_2O_3$[a)]

Aromatics	°C/h	Product	Yield (%)[b)]
	80/2		98
	50/2		96
	80/16		100
	50/2		92
	80/2		95
	50/2		81
	80/6		97

a) Solvent : Carbon tetrachloride; $CuBr_2$/aromatics=5. b) GC

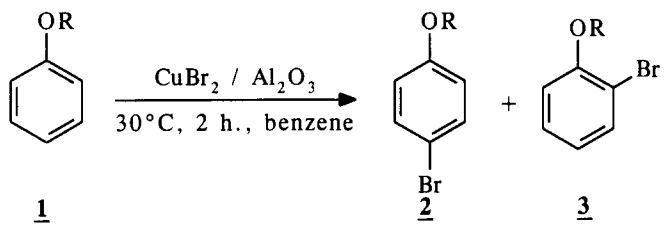
We postulated a reaction mechanism with participation of an aromatic radical cation which was formed by one electron transfer from an aromatic hydrocarbon to copper(II) chloride. Activated alumina has electron-acceptor properties, and formation of a radical cation of an aromatic hydrocarbon adsorbed on alumina has been observed by ESR (ref. 13). Therefore, it seemed to us that alumina as a support facilitates the generation of the radical cation of the aromatic hydrocarbon.

BROMINATION OF ALKOXYCOMPOUNDS

Bromination of Alkoxybenzenes

Alkoxybenzenes were highly regioselectively halogenated by use of copper(II) halides supported on alumina to give 4-halo-alkoxybenzenes in high yield. Bromination of alkoxybenzenes with alumina-supported copper(II) bromide occurred at lower temperature than chlorination with alumina-supported copper(II) chloride (ref. 14).

The reaction of anisole with copper(II) bromide in benzene at 50°C yielded no detectable products after 10 h. In contrast, in a similar reaction using alumina-supported copper(II) bromide, p-bromoanisole in 90 % yield was obtained from the reaction run at 30°C for 2 h. (eqn. 1). No dibromides were detected.



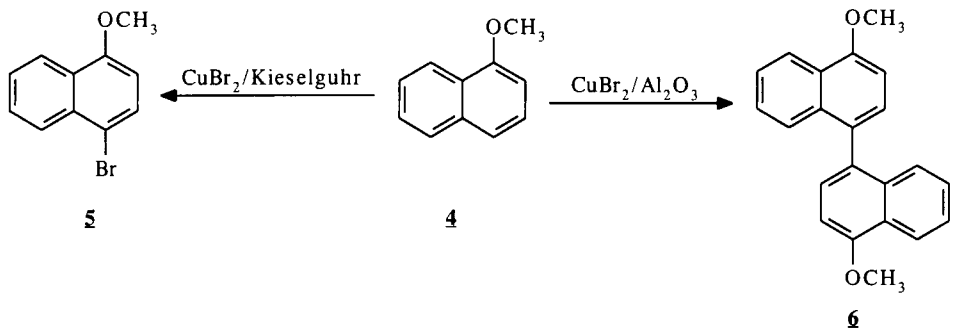
1 2 3 (1)

	Yield (%)	
	2	**3**
R = Methyl	90	0
Ethyl	92	3
Propyl	90	5
Butyl	93	2
Pentyl	93	2

The yield increased with increasing the ratio of alumina-supported copper(II) bromide to alkoxybenzenes. The size of alkoxy group did not influence significantly the yield and the ratio of p/o. Nonpolar solvents such as benzene and hexane were better than polar solvent. Polar solvents such as chloroform and tetrahydrofuran decreased the yield. It is suggested that these polar solvents may be strongly adsorbed on the surface of the reagent. The reaction did not proceed in ethanol to be due to the elution of copper(II) bromide from the alumina to the solution. It is known that the reaction of aromatic hydrocarbons with copper(II) halides in nonpolar solvents proceeds between aromatic hydrocarbons and solid copper(II) halides and not between hydrocarbons and dissolved copper(II) halides (ref. 6).

Bromination of 1-Alkoxynaphtalenes

The reaction of 1-alkoxynaphtalenes with copper (II) bromide in benzene produced a mixture of 4-bromo-1-alkoxynaphtalenes and 4,4'-dialkoxy-1,1'-binaphtyls. For instance, the reaction of 1-methoxynaphtalene **4** with copper(II) bromide in refluxing benzene for 2 h. gave a mixture of 4-bromo-1-methoxy-naphtalene **5** (47 %) and 4,4'-dimethoxy-1,1'-binaphtyl **6** (45 %). In contrast, in similar reaction using alumina-supported copper(II) bromide at 30°C, only dimerization occurred and no brominated compounds were obtained.



5 **4** **6**

Scheme 2. Reaction of methoxynaphtalene with $CuBr_2$ / Support

Silica gel and graphite were also effective as a support to give the binaphtyl preferentially, but the selectivity was lower than that of alumina. On the other hand, in similar reaction using Kieselguhr-supported copper(II) bromide, only 4-bromo-1-methoxynaphtalene was obtained in 92 % yield. The yield of the binaphthyl was negligible. The yield of the monobromide increased with increasing the ratio of Kieselguhr-supported copper(II) bromide to 1-methoxynaphtalene. Nonpolar solvents such as benzene were better than polar solvents. Polar solvents such as chloroform and tetrahydrofuran decreased the yield. The reaction did not proceed in ethanol to be due to the elution of copper(II) bromide from the Kieselguhr into the solution.

Table 3. Reaction of 1-Methoxynaphtalene with $CuBr_2$/Support[a)]

Support	Molar ratio of $CuBr_2$/4	Time/h	Yield % 5[b)]	6[c)]
none[d)]	2	4	47	45
Kieselguhr	1.5	1	40	tr[e)]
	3.0	3	92	tr
Alumina	1.5	1	tr	87
Silica gel	1.5	1	18	69
Graphite	1.5	1	17	76

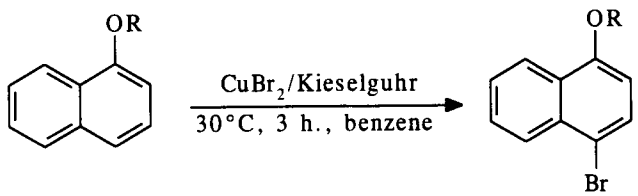
a) All reactions were carried out at 30°C in benzene b) By GC
c) Isolated yield d) Reflux e) tr indicates that the yield is less than 1 %.

These reactions are postulated to proceed by electro-transfer to give the radical cation of alkoxynaphtalene, which either undergoes reaction with copper(II) bromide or dimerizes (ref. 15). That is, one-electron transfer from the electron-rich alkoxynaphtalene to Cu(II) results in generation of the corresponding radical cation. The radical cation reacts with bromide anion leading to the brominated compound, whereas the radical cation undergoes reaction with another alkoxynaphtalene leading to the binaphtyl (eqns. 2-4).

$$C_{10}H_7OR \xrightarrow[-\ Cu(I)]{Cu(II)} C_{10}H_7OR^+ \qquad (2)$$

$$C_{10}H_7OR^+ + C_{10}H_7OR \longrightarrow ROC_{10}H_6-\overset{H}{\underset{H}{C}}-C_{10}H_6OR \qquad (3)$$

$$\xrightarrow[-\ Cu(I)]{Cu(II)} \xrightarrow{-\ 2H^+} ROC_{10}H_6C_{10}H_6OR \qquad (4)$$



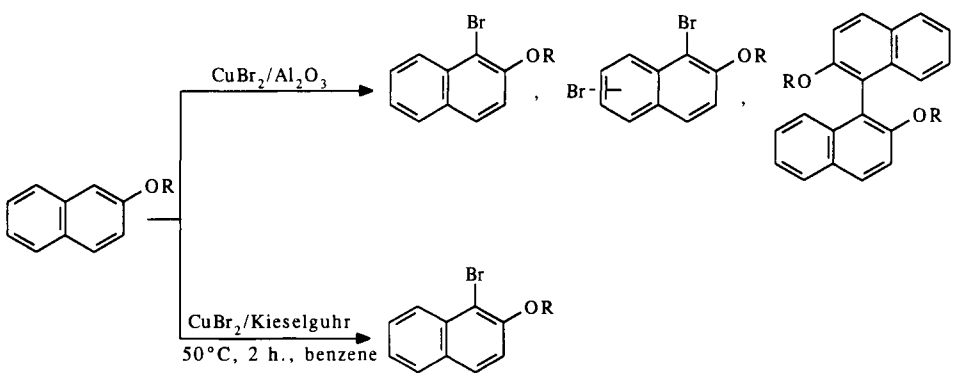
(5)

R =	Yield (%)
Ethyl	93
Propyl	92
Butyl	93
Hexyl	95

Bromination of 2-Alkoxynaphtalenes

2-Alkoxybenzenes were easily brominated under mild conditions by use of alumina or Kieselguhr-supported copper(II) bromide to give 1-bromo-2-alkoxy-naphtalenes in high yields. Alumina was more effective in activating copper(II) bromide than Kieselguhr. The reaction of 2-alkoxynaphtalenes with alumina-supported copper(II) bromide proceeded even at 10°C to give in addition to monobrominated compounds, dibromides and binaphtyls. In contrast to this reaction, reaction using Kieselguhr-supported copper(II) bromide at 50°C gave only 1-bromo-2-alkoxynaphtalenes in high yields.

For example, while reaction of 2-butoxynaphtalene with copper(II) bromide in benzene at 50°C for 2 h. produced only 6 % yield of 1-bromo-2-butoxynaphtalene, similar reaction with Kieselguhr-supported copper(II) bromide gave 86 % yield of the monobromide. On the other hand, reaction using alumina as a support in benzene proceeded completely even at 10°C in 1 h. to give in addition to the monobromide (77 %), the dibromide (21 %) and the binaphtyl (2 %).

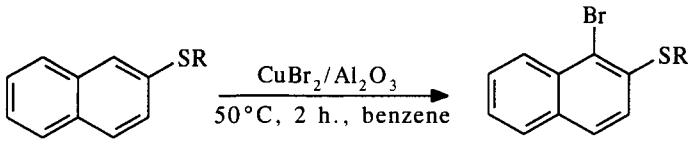


R =		
	Methyl	89 %
	Ethyl	90 %
	Butyl	86 %
	Hexyl	90 %

Scheme 3. Bromination of 2-Alkoxynaphtalenes with $CuBr_2$ / Support

Bromination of Alkylthionaphtalenes

Alkylthionaphtalenes reacted with alumina-supported copper(II) bromide to give monobrominated compounds in high yields and dimerization of alkylthionaphtalenes did not occur.



(6)

R =		Yield (%)
	Methyl	92
	Propyl	86
	Isobutyl	90

The reaction of 2-methylthionaphtalene with copper(II) bromide in benzene at 50°C yielded no detectable products after 5 h. In contrast, in similar reaction using alumina-supported copper(II) bromide, 1-bromo-2-methylthionaphtalene was obtained in 92 % yield after 1 h. Although 1-methoxynaphtalene reacted with alumina-supported copper(II) bromide to give only the binaphtyl, reaction of 1-methylthionaphtalene with alumina-supported copper(II) bromide afforded only 4-bromo-1-methylthionaphtalene (75 %) and the dimerization did not take place.

The usual aromatic bromination are performed by free bromine in the presence of a catalyst, most often iron. However, liquid bromine is not easy to handle because of its volatile and toxic character. On the other hand, alumina-supported copper(II) bromide can be treated easily and safely as a solid brominating reagent for aromatic compounds. The advantages of this procedure using the solid reagent are simple workups, mild conditions, and higher selectivities. Products can be isolated in good yield by simple filtration and solvent evaporation, and no extraction steps are required.

EXPERIMENTAL

Preparation of Copper(II) Bromide Supported on Alumina

To a solution of copper(II) bromide (10 g) in distilled water (30 ml) was added neutral alumina (20 g, Woelm N-super 1) at room temperature. The water was eveporated by using a rotary evaporator at 80°C under reduced pressure. The resulting reagent was then dried under vacuum (4 Torr) at 100°C for 15 h.

4-Bromo-m-xylene : General Procedure for Bromination of Polymethylbenzene

A mixture of m-xylene (2,4 g, 22.6 mmol), alumina-supported copper(II) bromide (50.5 g), and carbon tetrachloride (60 ml) was placed in a 100 ml round-bottom flask and stirred with a Teflon-coated magnetic stirring bar at 80°C for 1 h.

The products mixture was filtered, and the spent and unused reagent were washed with carbon tetrachloride (30 ml). The solvent was evaporated from the combined filtrate under reduced pressure, and the residue was distilled under vacuum to give 3.6 g (86 %) of 4-bromo-m-xylene. Bp 89-91°C/14 Torr (lit. 203°C (ref. 16)).

2,7-Dibromofluorene : General Procedure for Bromination of Polycyclic Aromatic Hydrocarbons

A mixture of fluorene (1.5 g, 9 mmol), alumina-supported copper(II) bromide (30 g), and carbon tetrachloride (80 ml) was placed in a 200 ml round-bottomed flask and stirred with a Teflon-coated magnetic stirring bar at 80°C for 5 h. The product mixture was filtered, and the spent reagent was washed with carbon tetrachloride (30 ml). Evaporation of solvent from the combined filtrate under reduced pressure yielded 2.84 g (97 %) of 2.7-dibromofluorene as a pale yellow solid having ^{1}H NMR and IR spectra identical with those of an authentic sample, mp 157-159°C (lit. mp 162-163°C (ref. 17)). The purity was > 96 % (GC).

4-Bromo-1-methoxynaphtalene : General Procedure for Bromination of 1- and 2-Alkoxynaphtalenes

A mixture of 1-methoxynaphtalene (1.90 g, 12 mmol) and Kieselguhr-supported copper(II) bromide (24 g) in benzene (150 ml) was stirred at 30°C for 3 h. The mixture was filtered, and the spent reagent was washed with benzene. The combined filtrate was concentrated, and the residue was distilled under vacuum to give 2.3 g (85 %) of 4-bromo-1-methoxynaphtalene. Bp 155-157°C/5 Torr (lit. 159-160°C/5 Torr (ref. 15)).

4,4'-Diethoxy-1,1-Binaphtyl

A mixture of 1-methoxynaphtalene (0.95 g, 6 mmol) and alumina-supported copper(II) bromide (6 g) in benzene (30 ml) was stirred at 30°C for 1 h. The mixture was filtered and the spent reagent was washed several times with hot benzene. Hexane was added to the combined filtrates, which was concentrated, to precipitate 4,4'-dimethoxy-1,1'-binaphtyl (0.82 g, 87 %), mp 254-255°C (from hexane-benzene (lit. 252-254°C (ref. 15)).

1-Bromo-2-methoxynaphtalene : General procedure for Bromination of Alkyl-thionaphtalene

A mixture of 2-methylthionaphtalene (0.52 g, 3 mmol) and alumina-supported copper(II) bromide (6 g) in benzene (30 ml) was stirred at 50°C for 2 h. The mixture was filtered and the spent reagent was washed with benzene. The combined

filtrate was evaporated and the residue recrystallized from ethanol giving 1-bromo-2-methylthionaphtalene (0.70 g, 92 %), mp 73-74°C.

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BROMINATION AND OXIDATION WITH BENZYLTRIMETHYL-AMMONIUM TRIBROMIDE

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ABSTRACT

Our recent studies on effective bromination and oxidation using benzyltrimethylammonium tribromide (BTMA Br_3), stable solid, are described. Those involve electrophilic bromination of aromatic compounds such as phenols, aromatic amines, aromatic ethers, acetanilides, arenes, and thiophene, α-bromination of arenes and acetophenones, and also bromo-addition to alkenes by the use of BTMA Br_3. Furthermore, oxidation of alcohols, ethers, 1,4-benzenediols, hindered phenols, primary amines, hydrazo compounds, sulfides, and thiols, haloform reaction of methylketones, N-bromination of amides, Hofmann degradation of amides, and preparation of acylureas and carbamates by the use of BTMA Br_3 are also presented.

INTRODUCTION

Since treatment of bromine as a brominating agent is not always ease because of its volatile and toxic characters, many attempts to develop a stable solid agent in place of liquid bromine have been undertaken.

As these solid agents, some quaternary ammonium tribromides such as pyridinium hydrobromide perbromide (ref. 1), phenyltrimethylammonium tribromide (ref. 2), tetramethylammonium tribromide (ref. 3), and tetrabutyl-ammonium tribromide (ref. 4) have already been reported as mild and selective brominating agents (Fig. 1).

During the course of our investigation dealing with these quaternary ammonium

tribromides, we found that benzyltrimethylammonium tribromide is most useful brominating and oxidizing agent among these salts. In this report, we will describe the bromination and oxidation with mainly benzyltrimethylammonium tribromide (BTMA Br_3), according to the next order ; (i) electrophilic bromo-substitution of aromatic compounds, (ii) side-chain bromination of aromatic compounds, (iii) bromo-addition to unsaturated bonds, and then (iv) oxidation.

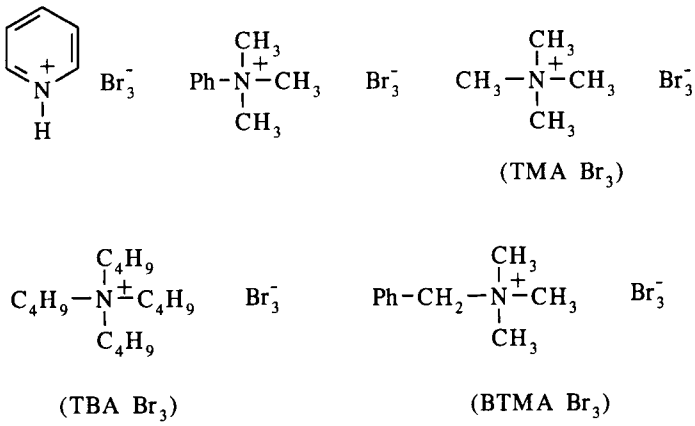

Fig. 1. Quaternary ammonium tribromides

Incidentally, the term "halogenation" can be classified within the general category of "oxidation". However, in this report, we define "halogenation" as the chemical combination of a carbon atom with a halogen atom, and "oxidation" as the combination of a heteroatom such as a nitrogen-, oxygen-, or sulfur-atom with a halogen. Accordingly, we will deal with "N-bromination of amides" in the "oxidation" section.

PREPARATION OF BENZYLTRIMETHYLAMMONIUM TRIBROMIDE AND ITS PHYSICAL PROPERTIES

The reaction of benzyltrimethylammonium bromide with bromine in dichloromethane gave BTMA Br_3, which was also prepared by the addition of hydrobromic acid to an aqueous solution of benzyltrimethylammonium chloride and sodium bromate in good yield (Fig. 2) (ref. 5) : stable orange red needles, mp 100-101°C; soluble in CH_2Cl_2, DMSO, and DMF, slightly soluble in MeOH, AcOH, AcOEt, and $CHCl_3$, insoluble in C_6H_{14}, C_6H_6, CCl_4, and H_2O. Still, this compound slightly decompose under standing for a long time in contact with air or

water. Recently, we confirmed that Br_3-anion posseses a linear structure as shown in its ORTEP drawing (Fig. 3).

$$PhCH_2Me_3NBr + Br_2 \longrightarrow PhCH_2Me_3NBr_3$$

$$PhCH_2Me_3NCl + 1/2\ NaBrO_3 + 7/2\ HBr \longrightarrow PhCH_2Me_3NBr_3 + 1/2\ NaCl + 1/2\ HCl + 1/2\ Br_2 + 3/2\ H_2O$$

Fig. 2. Preparation of BTMA Br_3

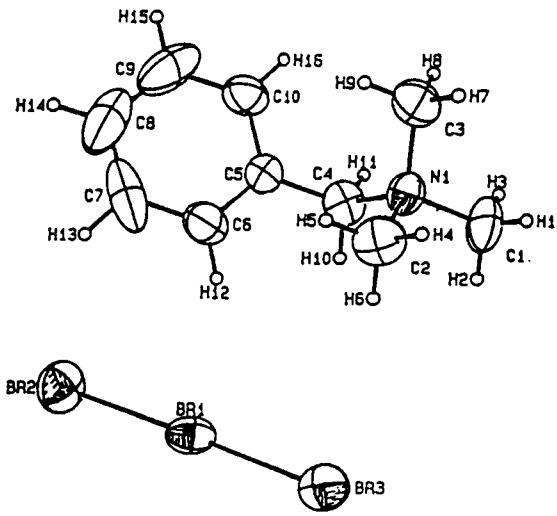

Fig.3. Crystal structure of BTMA Br_3

ELECTROPHILIC BROMO-SUBSTITUTION OF AROMATIC COMPOUNDS

Bromination of phenols

In general, it is difficult to carry out a step-by-step bromination of phenols with bromine, since phenols react very rapidly with bromine, which leads to the polybromo-substituted phenols. We found that the reaction of phenols with calculated amounts of tetrabutylammonium tribromide (TBA Br_3) or BTMA Br_3 in

dichloromethane-methanol at room temperature gave the desirable mono-, di-, or tribromo-substituted phenols, selectively (Fig. 4). For instance, reactions of phenol with 1 equiv. of TBA Br_3 gave 4-bromophenol, and with 2 equiv. of BTMA Br_3 gave 2,4-dibromophenol; furthermore, reactions with 3 equiv. of BTMA Br_3 gave 2,4,6-tribromophenol in good yields, respectively (ref. 6).

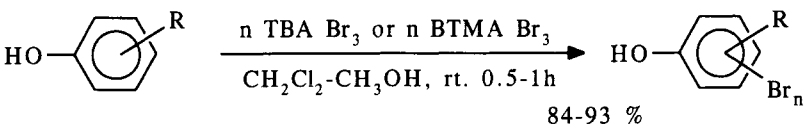

Fig. 4. Bromination of Phenols with TBA Br_3 or BTMA Br_3

Because the presence of methanol markedly facilitates the bromination of phenols, we decided that the active species is probably methyl hypobromite produced by the reaction of these tribromides with methanol as shown below (Fig. 5) (ref. 7).

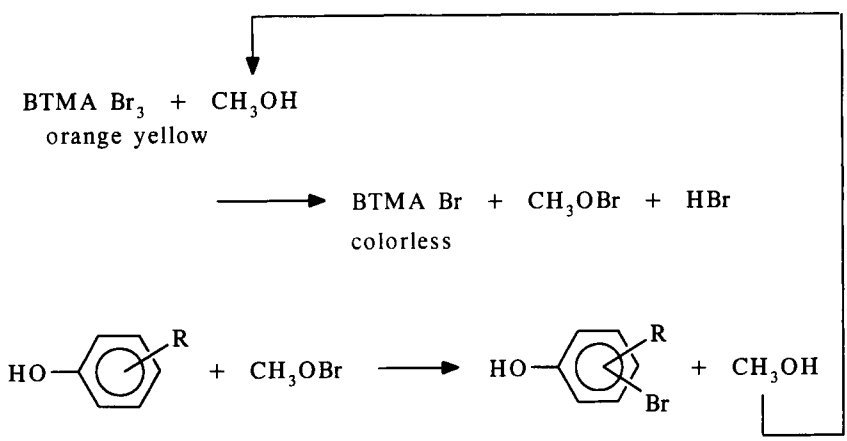

Fig. 5. Generation of active species CH_3OBr, and reaction of phenols with CH_3OBr

Styrene polymer-bound benzyltrimethylammonium tribromide is also used as the brominating agent. The polymeric agent was easily prepared from AGI-X_2 as shown in Fig. 6. Passing a solution of phenols in dichloromethane-methanol through a column packed with the polymeric agent at room temperature gave bromo-substituted phenols in quantitative yields. The polymer is transformed into a colorless Ⓟ— BTMA Br which can be easily regenerated back into a polymeric

agent by passing a solution of bromine in dichloromethane through the column (Fig. 7) (ref. 8).

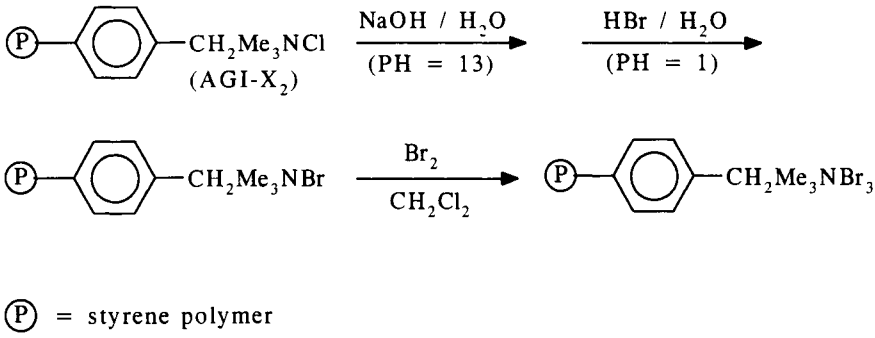

Fig. 6. Preparation of styrene polymer-bound BTMA Br_3

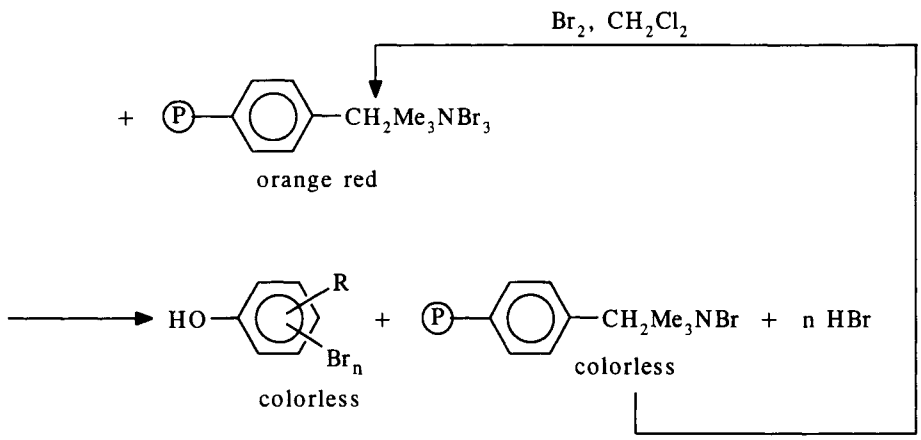

Fig. 7. Bromination of phenols with styrene polymer-bound BTMA Br_3

Recently, Smith et al. reported that the reaction of phenols with a calculated amount of the polymer-bound BTMA Br_3 gave p-monobromo-substituted phenols, selectively (ref. 9).

Bromination of aromatic amines

Berthelot et al. have already reported that the reaction of aromatic amines with tetrabutylammonium tribromide (TBA Br_3) in chloroform gave p-selective bromo-substituted aromatic amines (ref. 10). We also carried out the bromination of

aromatic amines using BTMA Br_3. That is, the reaction of aromatic amines with BTMA Br_3 in dichloromethane-methanol containing calcium carbonate powder for 0.5 h at room temperature gave bromo-substituted aromatic amines in good yields. In these cases, calcium carbonate was used in order to neutralize a generating hydrogen bromide, and the reaction was remarkably enhanced by the presence of methanol (Fig. 8) (ref. 11).

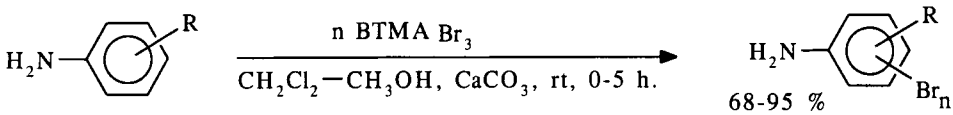

Fig. 8. Bromination of aromatic amines with BTMA Br_3

Furthermore, styrene polymer-bound BTMA Br_3 was also used as the reagent for the preparation of polybromo-substituted aromatic amines (ref. 12).

Bromination of aromatic ethers

In general, it is not easy to prepare bromo-substituted aromatic ethers through the electrophilic substitution of aromatic ethers with free bromine, in spite of the presence of moderately active alkoxy groups in their molecules. Recently, Berthelot et al. reported that although phenols underwent p-selective monobromination by an equimolar amount of TBA Br_3, bromination of methoxybenzene with TBA Br_3 under the same conditions did not proceed at all (ref. 13). However, we found that in the presence of methanol, bromination of methoxybenzene with TBA Br_3 readily proceeded at room temperature. Thus, we found that tetraalkylammonium polyhalides such as TBA Br_3, BTMA Br_3, BTMA Br_2Cl, and BTMA $BrCl_2$ in dichloromethane-methanol, acted as excellent brominating agents for aromatic ethers. That is, the reaction of aromatic ethers with these agents in dichloromethane-methanol at room temperature gave bromo-substituted aromatic ethers in good yields (Fig. 9). In these cases, monobromides have usually been obtained from the reaction of aromatic ethers with TBA Br_3, BTMA Br_3, and BTMA Br_2Cl, whereas dibromides could be obtained by using BTMA $BrCl_2$. Thus, we found that the reactivity of these agents for the bromination of aromatic ethers follows the order of TBA Br_3 < BTMA Br_3 < BTMA Br_2Cl < BTMA $BrCl_2$ (ref. 14).

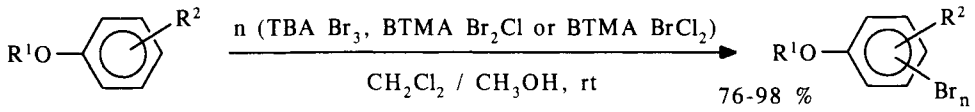

Fig. 9. Bromination of aromatic ethers with several polyhalides

Furthermore, the reaction of aromatic ethers with a stoichiometric amount of BTMA Br_3 in dichloromethane-methanol or acetic acid-zinc chloride under mild conditions gave, selectively, mono-, di-, or tribromo-substituted aromatic ethers in quantitative yields (Fig. 10) (ref. 15).

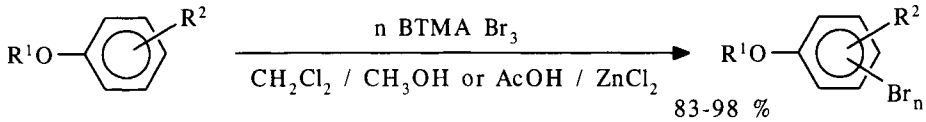

Fig. 10. Selective bromination of aromatic ethers with BTMA Br_3

Incidentally, BTMA Br_3 is only slightly soluble in acetic acid at room temperature, but the addition of $ZnCl_2$ increases its solubility, allowing the bromination of aromatic ethers to proceed smoothly under mild conditions. An equimolar amount of $ZnCl_2$ with respect to BTMA Br_3 is required. We proposed the existence of the complex as the active species, formed from BTMA Br_3 and an equimolar amount of $ZnCl_2$, as shown in Fig. 11. It turned out that $ZnCl_2$ was a more effective Lewis acid that $AlCl_3$, $AlBr_3$, $FeCl_3$, and $ZnBr_2$ (ref. 15, 16).

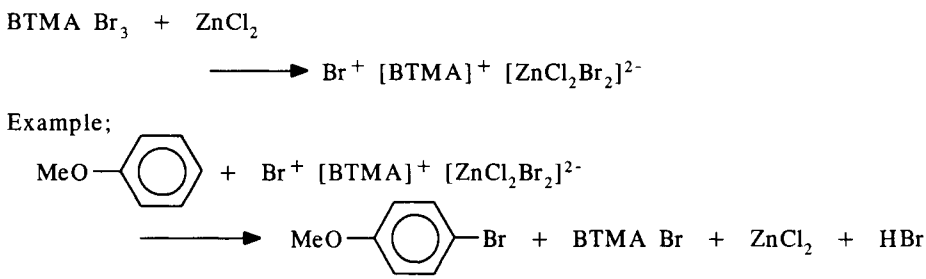

Fig. 11. Proposed active species from BTMA Br_3 and $ZnCl_2$

Bromination of acetanilides

The reaction of acetanilides with tetraalkylammonium polyhalides, such as TBA Br_3, BTMA Br_3, or BTMA Br_2Cl in dichloromethane-methanol at room temperature gave bromo-substituted acetanilides in good yields, respectively. These bromination of acetanilides have usually given predominantly the corresponding p-bromo derivatives (Fig. 12) (ref. 17). Furthermore, the reaction of acetanilides with BTMA Br_3 in acetic acid in the presence of $ZnCl_2$ gave polybromo-substituted acetanilides which was not obtained from the reactions in dichloromethane-methanol (ref. 18).

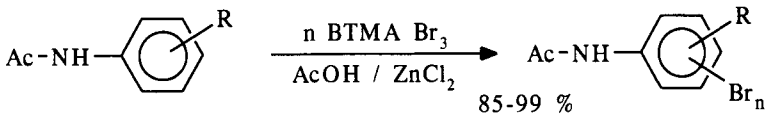

Fig. 12. Bromination of acetanilides with BTMA Br_3

Bromination of arenes

Combined effect of BTMA Br_3 and $ZnCl_2$ in acetic acid provides a new excellent bromination procedure for arenes. That is, while such reactive aromatic compounds as phenols, aromatic amines, aromatic ethers, and acetanilides have been easily brominated by BTMA Br_3 in dichloromethane in the presence of methanol, the reaction of arenes, less reactive compounds, with BTMA Br_3 in dichloromethane-methanol did not proceed at all, even under reflux for many hours. However, arenes could be smoothly brominated by use of this agent in acetic acid with the aid of the Lewis acid $ZnCl_2$ (Fig. 13) (ref. 16).

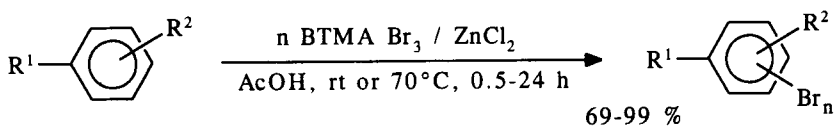

Fig. 13. Bromination of arenes with BTMA Br_3

Bromination of thiophene derivatives

Since thiophene derivatives, heterocyclic aromatic compounds, are sensitive toward electrophilic substitution reactions, the bromination of these compounds generally gives a mixture of mono-, di-, and other poly-substituted bromination products (ref. 19). However, we have recently found that BTMA Br_3 is a useful

agent for the bromination of thiophene derivatives. The reaction of thiophene derivatives with BTMA Br_3 in acetic acid in the presence of $ZnCl_2$ under mild conditions gave bromo-substituted thiophene derivatives in satisfactory yields (Fig. 14) (ref. 20).

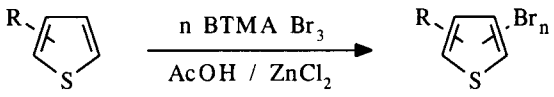

Fig. 14. Bromination of thiophene derivatives with BTMA Br_3

SIDE-CHAIN BROMINATION OF AROMATIC COMPOUNDS

Benzylic bromination of arenes

Usually, α-bromo-substituted arenes have been prepared through the reaction of arenes with bromine under ultraviolet irradiation. In the presence of benzoyl peroxide, N-bromosuccinimide can also be used for this purpose.

Avramoff et al. have already reported that the reaction of hydrocarbons such as toluene with tetramethylammonium tribromide (TMA Br_3) in benzene, in the presence of benzoyl peroxide at room temperature gave benzylic bromination products (ref. 21). However, TMA Br_3 is not easy to handle in comparison with the stable BTMA Br_3 because of its hydroscopic character. Furthermore, as shown in their literature, a large excess of TMA Br_3 is necessary to brominate arenes.

We found that the reaction of arenes with a calculated amount of BTMA Br_3 in refluxing benzene in the presence of AIBN gave α-bromo-substituted arenes in fairly good yields. In this method, it was found that AIBN was a more effective free radical initiator than benzoyl peroxide (Fig. 15) (ref. 22).

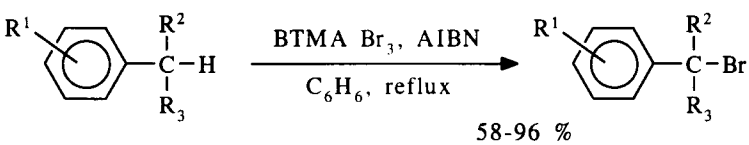

Fig. 15. Benzylic bromination of arenes with BTMA Br_3

α-Bromination of acetophenone derivatives

Djerassi et al. have already demonstrated the use of pyridinium hydrobromide perbromide for efficient α-bromination of steroid ketones (ref. 23). Cacchi et al.

have also reported the α-bromination of steroid ketones by using styrene polymer-bound BTMA Br_3 (ref. 24).

Similarly, we found that quaternary ammonium tribromides such as TBA Br_3 and BTMA Br_3 are useful agents for the α-bromination of acetyl derivatives (Fig. 16) (ref. 25).

$$Ar-COMe \xrightarrow[CH_2Cl_2 \,/\, CH_3OH,\ rt]{TBA\ Br_3} Ar-COCH_2Br \quad (71\text{-}99\ \%)$$

Fig. 16. α-Bromination of acetophenone derivatives with TBA Br_3

Furthermore, the reaction of acetophenone derivatives with 2 equiv. of BTMA Br_3 gave α, α-dibromo-substituted acetophenone derivatives in good yields (Fig. 17). In these cases, when an equimolar amount of BTMA Br_3 was used with acetophenone derivatives, monobromoacetyl derivatives were obtained in the same manner as when using TBA Br_3. However, the reaction of acetophenone derivatives with 2 equiv of TBA Br_3 gave monobromoacetyl derivatives as the main product together with dibromoacetyl derivatives as by-product. That is, as shown before, we found that BTMA Br_3 is a stronger brominating agent than TBA Br_3 (ref. 5).

$$Ar-COMe \xrightarrow[CH_2Cl_2 \,/\, CH_3OH,\ rt]{2\ BTMA\ Br_3} Ar-COCHBr_2 \quad (75\text{-}89\ \%)$$

Fig. 17. α, α-Dibromination of acetophenone derivatives with BTMA Br_3

BROMO-ADDITION TO UNSATURATED BONDS

Fieser et al. have already found that bromination of trans-stilbene with pyridinium hydrobromide perbromide in acetic acid gave exclusively meso-stilbene dibromide, and have further shown that the agent possesses far greater stereoselectivity than free bromine (ref. 26). Fournier et al. have reported the bromo-addition to double-bond of several alkenes by use of TBA Br_3 (ref. 27). Moreover, Bethelot et al. described the bromo-addition to triple-bond of alkynes with TBA Br_3 (ref. 28).

We have investigated the bromo-addition of alkenes and their related compounds with BTMA Br_3. Thus, we found that the reaction of alkenes with BTMA Br_3 in aprotic solvents such as dichloromethane and chloroform gave 1,2-dibromo adducts in a manner of stereospecific anti-addition, and, in such protic solvents as methanol and acetic acid, gave the corresponding dibromo adducts along with considerable amounts of solvent-incorporated products in regioselective manner (Fig. 18) (ref. 29).

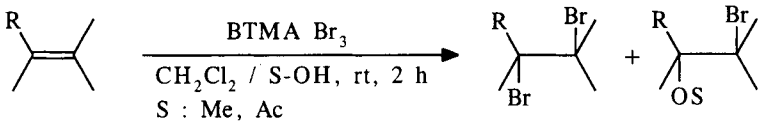

Fig. 18. Bromo-addition to double-bond with BTMA Br_3 in protic solvents

Moreover, Negoro et al. reported that the reaction of alkenes and their related compounds with tetrabutylammonium dichlorobromate (TBA $BrCl_2$) in chloroform gave bromochloro-adducts through stereospecific anti-addition (Fig. 19) (ref. 30).

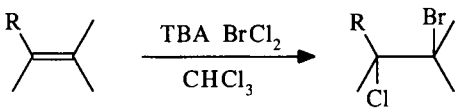

Fig. 19. Bromochloro-addition to double-bond with TBA $BrCl_2$

OXIDATION WITH BENZYLTRIMETHYLAMMONIUM TRIBROMIDE

Oxidation of alcohols and ethers

There are a number of methods for the oxidation of primary alcohols or ethers to dimeric esters, and secondary alcohols to ketones. We recently also found that quaternary ammonium tribromides, especially BTMA Br_3, are useful oxidizing agents for the purpose described above (ref. 31).

That is, the reaction of primary alcohols or ethers with a calculated amount of BTMA Br_3 in carbon tetrachloride-water in the presence of Na_2HPO_4 at 60°C gave dimeric esters in good yields. In the case of benzyl alcohol, the only oxidation product was benzaldehyde (Fig. 20).

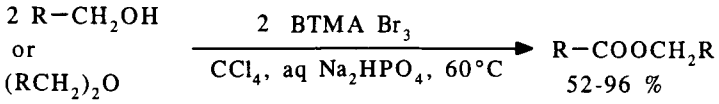

Fig. 20. Oxidation of primary alcohols and ethers with BTMA Br_3

The reaction scheme is as follows (Fig. 21). It is reasonable to assume that BTMA Br_3 can be dissociated by water as shown in Equation 1. The resulting hypobromous acid may act as the major active oxidizing species and may convert alcohols into esters as Equation 2. In the case of ethers, we can show as Equation 4. Generated hydrobromic acid can be removed by Na_2HPO_4 which has been added previously (Eqn. 5).

$$\text{BTMA } Br_3 + H_2O \longrightarrow \text{BTMA Br} + \text{HOBr} + \text{HBr} \quad (1)$$

$$R{-}CH_2OH + 2\ \text{HOBr} \longrightarrow R{-}COOCH_2R + 2\ H_2O + 2\ \text{HBr} \quad (2)$$

Overall;

$$2\ R{-}CH_2OH + 2\ \text{BTMA } Br_3 \longrightarrow R{-}COOCH_2R + 2\ \text{BTMA Br} + 4\ \text{HBr} \quad (3)$$

In the case of ethers;

$$R{-}CH_2OCH_2R + 2\ \text{BTMA } Br_3 + H_2O \longrightarrow R{-}COOCH_2R + 2\ \text{BTMA Br} + 4\ \text{HBr} \quad (4)$$

$$\text{HBr} + Na_2HPO_4 \longrightarrow NaH_2PO_4 + \text{NaBr} \quad (5)$$

Fig. 21. Reaction scheme for the oxidation of alcohols and ethers with BTMA Br_3

The reaction of α, ω-diols or cyclic ethers with a stoichiometric amount of BTMA Br_3 in carbon tetrachloride, or in acetic acid in the presence of aqueous Na_2HPO_4 or CH_3COONa, at 60-70°C gave lactones. The results are shown in Figure 22.

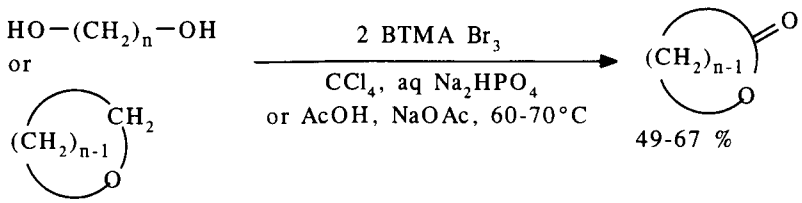

Fig. 22. Lactonization of α, ω-diols and cyclic ethers with BTMA Br_3

Furthermore, the oxidation of secondary alcohols with an equimolar amount of BTMA Br_3 in the presence of a buffer such as aq. Na_2HPO_4 or aq. CH_3COONa afforded the corresponding ketones in good yields (Fig. 23).

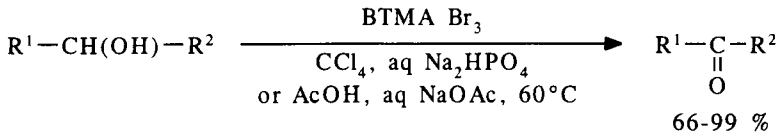

Fig. 23. Oxidation of secondary alcohols with BTMA Br_3

Although a variety of substituted benzyl alcohols have been converted into the corresponding benzaldehydes by means of a number of oxidizing agents, we have found that BTMA Br_3 is also a convenient reagent for oxidizing benzyl alcohols into benzaldehydes. That is, the reaction of benzyl alcohols with 1-equiv. of BTMA Br_3 in carbon tetrachloride in the presence of an aq. alkaline solution, an aq. solution of Na_2HPO_4, or water, at room temperature or at 70°C gave benzaldehyde in satisfactory yields.

We have also found that BTMA Br_3 can be used as a reagent for the oxidation of benzyl alcohols to benzoic acids. That is, the reaction of benzyl alcohols with 2-equiv. of BTMA Br_3 in an aq. alkaline solution at room temperature or at 70°C afforded benzoic acids in good yields. Thus, we could selectively obtain the oxidation products, benzaldehydes and benzoic acids, from benzyl alcohols by using a stoichiometric amount of BTMA Br_3 (Fig. 24) (ref. 32).

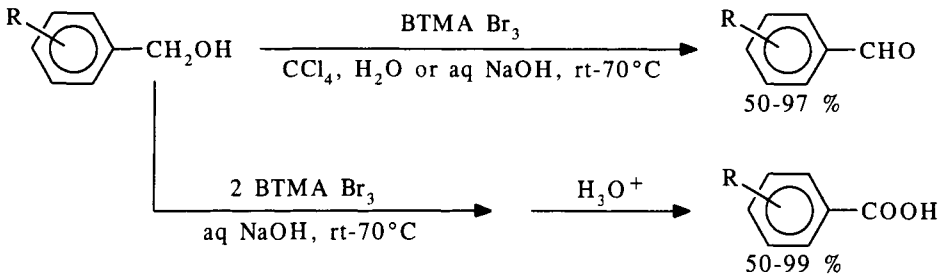

Fig. 24. Selective oxidation of benzyl alcohols with BTMA Br_3

Oxidation of 1,4-benzenediols and hindered phenols

The reaction of 1,4-benzenediols with an equimolar amount of BTMA Br_3 in dichloromethane in the presence of aq. sodium acetate at room temperature gave 2,5-cyclohexadiene-1,4-diones in good yields. On the other hand, the reaction of 1,4-benzenediols with a large excess of the agent in aq. acetic acid at 40-60°C gave polybromo-substituted products (Fig. 25) (ref. 33).

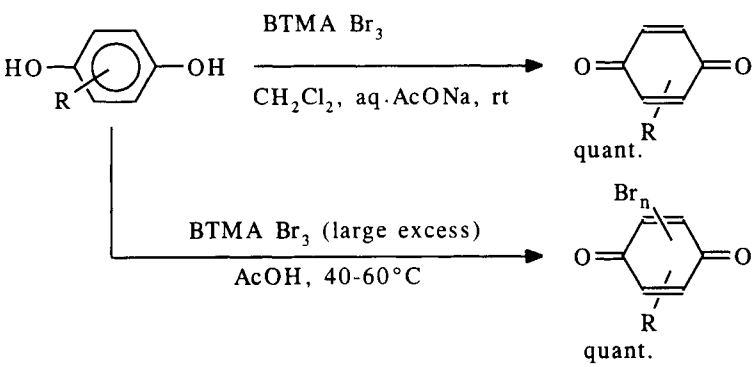

Fig. 25. Oxidation of 1,4-benzenediols with BTMA Br_3

Furthermore, the reaction of several hindered phenols, such as 2,6-di-t-butyl-4-methylphenol, 3,5-di-t-butyl-4-hydroxybenzyl alcohol, and 2,6-di-t-butylphenol, with BTMA Br_3 were carried out in dichloromethane in the presence of water, t-butyl alcohol, or aq. sodium hydroxide at room temperature. Sequential reaction processes were provided by the obtained products. As an example, we show the reaction of 2,6-di-t-butyl-4-methylphenol with BTMA Br_3 in Fig. 26 (ref. 34).

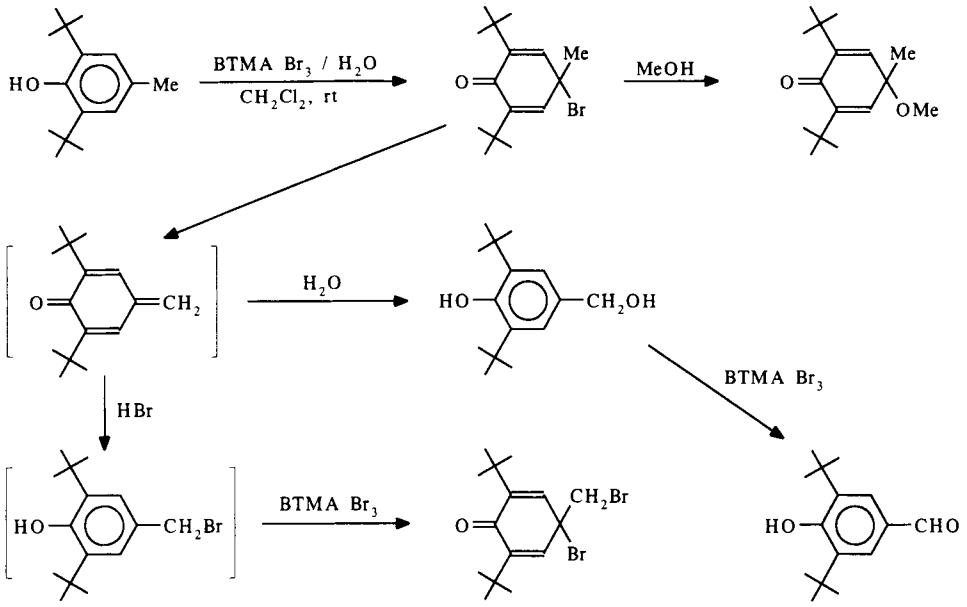

Fig. 26. Oxidation of 2,6-di-t-butyl-4-methylphenol with BTMA Br_3

Oxidation of primary amines and hydrazo compounds

It has already been known that the reaction of primary amines with alkaline hypobromite gives nitriles, and the reaction of hydrazo compounds with bromine affords azo compounds. Recently, we also found that the reaction of primary amines and hydrazo compounds with BTMA Br_3 in aq. sodium hydroxide or in water gave corresponding nitriles and azo compounds in satisfactory yields, respectively (Fig. 27) (ref. 35).

$$R-CH_2NH_2 \xrightarrow[\text{aq NaOH, 40°C, 7-12 h}]{\text{2 BTMA } Br_3} R-C\equiv N \quad 32\text{-}72\ \%$$

$$R-NH-NH-R \xrightarrow[CH_2Cl_2 \,/\, H_2O,\ \text{rt, 0.5 - 10 h}]{\text{BTMA } Br_3} R-N=N-R \quad 60\text{-}91\ \%$$

Fig. 27. Oxidation of primary amines and hydrazo compounds with BTMA Br_3

Oxidation of sulfides to sulfoxides and oxidation of thiols to disulfides

The oxidation of sulfides to sulfoxides are occasionally found to be unsatisfactory, since the resulting sulfoxides are easily oxidized to sulfones. In order to avoid the further oxidation of sulfoxides into sulfones, several oxidizing agents have been selected. Recently, we found that BTMA Br_3 is the most effective and satisfactory oxidizing agent for this purpose. That is, the reaction of sulfides with a calculated amount of BTMA Br_3 and aq. sodium hydroxide in dichloromethane at room temperature, or in 1,2-dichloroethane under reflux, gave sulfoxides in good yields (Fig. 28) (ref. 36).

$$R^1-S-R^2 \xrightarrow[CH_2Cl_2 \text{ rt, or } ClCH_2CH_2Cl \text{ reflux}]{\text{BTMA } Br_3, \text{ aq NaOH}} \underset{47 - 98\ \%}{R^1-SO-R^2}$$

Fig. 28. Oxidation of sulfides to sulfoxides with BTMA Br_3

Although the oxidation of thiols with chlorine or bromine in the presence of water gives sulfonyl halides or sulfonic acids, the reaction of thiols with a stoichiometric amount of BTMA Br_3 and sodium hydroxide in dichloromethane-water at room temperature gives disulfides in good yields (Fig. 29) (ref. 37).

$$2\ R-SH \xrightarrow[CH_2Cl_2,\ \text{rt, 10-20 min}]{\text{BTMA } Br_3, \text{ aq NaOH}} \underset{60\text{-}99\ \%}{R-S-S-R}$$

Fig. 29. Oxidation of thiols to disulfides with BTMA Br_3

Haloform reaction of methyl ketones

The reaction of methyl ketones with a calculated amount of BTMA Br_3 in aq. sodium hydroxide at room temperature and subsequent acid hydrolysis gave carboxylic acids together with bromoform in good yields. Aliphatic and aromatic methyl ketones have usually been reacted (Fig. 30) (ref. 38).

$$R-COMe \xrightarrow[\text{aq NaOH, rt}]{3\ \text{BTMA } Br_3} \xrightarrow{H_3O^+} \underset{52\text{-}99\ \%}{R-COOH} + CHBr_3$$

Fig. 30. Haloform reaction of methyl ketones with BTMA Br_3

N-Bromination of amides

The N-bromination of amides with bromine and alkali has been extensively researched as the first step of the Hofmann degradation. However, it is difficult to isolate the N-bromoamides because of their subsequent reaction to produce amines, which proceeds very readily under excessive alkaline conditions. Now, the reaction of amides with a stoichiometric amount of BTMA Br_3 and sodium hydroxide in ice-water gave N-bromoamides in fairly good yields. Our method can be applied to various types of aliphatic, aromatic, and heterocyclic amides (Fig. 31) (ref. 39).

$$R-CONH_2 \xrightarrow[\text{aq NaOH (ice cold)}]{\text{BTMA } Br_3,\ 30\ \text{min}} R-CONH-Br \quad 47\text{-}86\ \%$$

Fig. 31. N-Bromination of amides with BTMA Br_3

Hofmann degradation of amides

Although the Hofmann degradation of amides with an alkaline solution of bromine or chlorine gives amines, these methods are occasionally accompanied by problems in terms of satisfactory and reliable results. For that reason, several reagents have been used for the degradation of amides instead of free halogen. We have already reported that amides can be converted into amines by the use of commercial sodium bromite ($NaBrO_2$) (ref. 40). Recently, we have found that using BTMA Br_3 in aq. sodium hydroxide is the most effective and reproducible method. That is, the reaction of amides with a calculated amount of BTMA Br_3 and aq. sodium hydroxide at room temperature or at 70°C gave amines in fairly good yields. The reaction scheme can be presented in the following equation (Fig. 32), and the experimental results are briefly shown in Figure 33 (ref. 41).

$$R-CONH_2 + \text{BTMA } Br_3 + 4\ NaOH \longrightarrow R-NH_2 + \text{BTMA Br} + 2\ NaBr + Na_2CO_3 + 2\ H_2O$$

Fig. 32. Reaction scheme of the Hofmann degradation of amides with BTMA Br_3

$$R-CONH_2 \xrightarrow[\text{aq NaOH, 1-5 h}]{\text{BTMA } Br_3,\ \text{rt or } 70°C} R-NH_2 \quad 51\text{-}93\ \%$$

Fig. 33. Hofmann degradation of amides with BTMA Br_3

Preparation of acylureas and carbamates

The reaction of amides with half equiv. of BTMA Br_3 and one equiv. of DBU in dichloromethane-methanol at room temperature gave N-substituted acylureas in fairly good yields (Fig. 34). Furthermore, in the presence of a large excess of methanol, the reaction of amides with one equiv. of BTMA Br_3 and two equiv. of DBU in dichloromethane gave methyl carbamates as main products (Fig. 35). In these reactions, we assumed that in the presence of DBU, intermediary isocyanates react with excess of amides to afford acylureas, and react with excess of methanol to afford methyl carbamates (ref. 42).

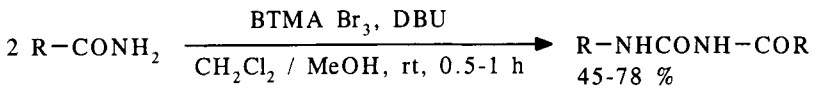

Fig. 34. Preparation of acylureas from amides with BTMA Br_3

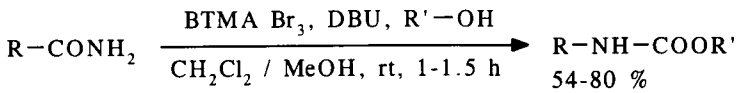

Fig. 35. Preparation of methyl carbamates from amides with BTMA Br_3

SUMMARY

Finally, we can consider that benzyltrimethylammonium tribromide (BTMA Br_3) is regarded as "solidified bromine". We now believe that in laboratory, BTMA Br_3 is more useful brominating and oxidizing agent than liquid bromine. This agent has some merits shown as follows. (1) This agent can be used stoichiometrically because of its stable solid character. (2) This agent can be easily prepared from cheap benzyltrimethylammonium salts and free bromine. (3) Usually, the reaction proceed under mild conditions. (4) The end point of the reaction can be detected by the decolorization of the agent. (5) Usually, reaction products are obtained in satisfactory yields. (6) Whether one carries out the reaction in dichloromethane-methanol or in acetic acid-zinc chloride, selective bromination is possible. (7) After the reaction has been complated, benzyltrimethylammonium bromide, starting material, can be readily recovered from the final aqueous solution.

ACKNOWLEDGMENTS

The research work described here was carried out by an able group of students of Yamaguchi University and Ube Techinical College, and in collaboration with our laboratory staffs and industrial colleagues. In particular, Dr. S. Fujisaki and Dr. T. Okamoto made significant contributions. We thank them all, and also Dr. H. Tsuzuki of Central Analytical Center of Kyushu University undertook X-ray crystal structure analysis of BTMA Br_3. Furthermore, we wish to thank Professor M. Tashiro of Kyushu University for useful discussions. Finally, we are grateful to Professor Y. Sasson of The Hebrew University of Jerusalem, Chairman of the Scientific Committee of Orgabrom'93, for the invitation to present this work in Jerusalem.

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ADVANCES IN THE SYNTHESIS AND APPLICATIONS OF ORGANOBROMINE COMPOUNDS

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SUMMARY

Bromination of toluene in quantitative yield and with excellent *para*-selectivity can be achieved by use of *tert*-butyl hypobromite in the present of proton-exchanged zeolite X. Highly *para*-selective bromination of phenols is possible with a polystyrene resin bearing tetraalkylammonium tribromide groups. Bromo-compounds produced in these or other ways are useful as substrates either in direct substitution reactions or *via* conversion into organometallic reagents and subsequent reactions with electrophiles. Interesting examples include the syntheses of diaryl ethers, highly hindered organoboron compounds, and indigo and related compounds.

INTRODUCTION

We have previously shown (ref. 1) that microporous solids are useful in the controlled bromination of aromatic substrates. In particular, we showed how a reagent system comprising *N*-bromosuccinimide (NBS) and silica is useful for the bromination of reactive aromatic systems such as indoles (Fig. 1) (ref. 2), carbazoles and iminodibenzyls (Fig. 2) (ref. 3).

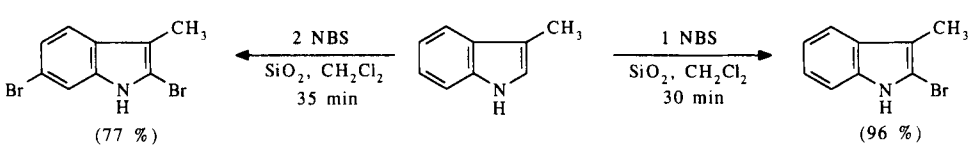


Fig. 1. Bromination of skatole by NBS-silica

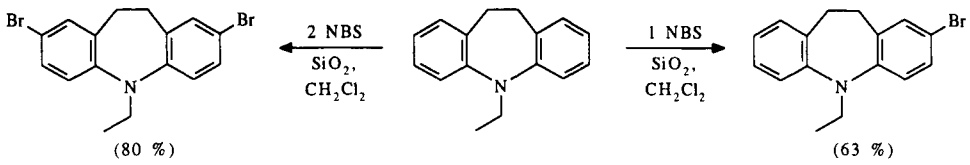


Fig. 2. Bromination of *N*-ethyliminodibenzyl with NBS-silica

Unfortunately, the reagent system was insufficiently reactive to provide a convenient method of bromination of moderately active substrates such as toluene and benzene. More reactive reagent systems were therefore developed in which the silica gel was replaced by a more acidic solid such as montmorillonite K10 or the NBS was replaced by a more active brominating agent (ref. 1). Such systems were sufficiently active to brominate toluene readily at ambient temperature, but unfortunately were no more regioselective than traditional methods of brominating toluene. One of the tasks of our recent research, therefore, was to develop a reagent system which took advantage of the properties of solids to gain such regioselective control.

By contrast, highly activated aromatic substrates such as phenols present problems associated with overbromination as well as lack of regioselectivity, both with traditional reagents and with reagent systems such as NBS-silica. We have previously developed a reagent system based on NBS and Amberlite A50 ion-exchange resin (Fig. 3) (ref. 1), but the method has not been generally applied and in any case is open to further improvement. Consequently, we have continued to study the use of solids for controlled bromination of such aromatic substrates and this report outlines some of our recent findings in this area.

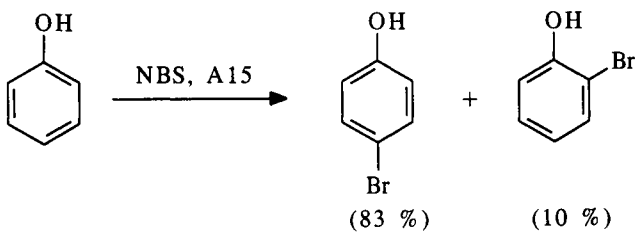


Fig. 3. Bromination of phenol with NBS-A15

The production of aromatic bromo-compounds is rarely an end in itself. More commonly the bromo-compounds are precursors for some further synthetic steps. Often, the bromine is replaced either in a direct substitution reaction or *via*

conversion of the bromo-compound into an organolithium or organomagnesium compound which is then reacted with an electrophile. This report also details recent examples of such applications.

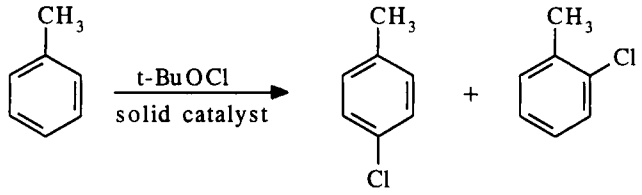
SELECTIVE BROMINATION OF AROMATIC SUBSTRATES

Selective Bromination of Toluene

Traditional methods for bromination of toluene with bromine and a catalyst result in relatively low *para*-selectivity. For example, bromine in acetic acid gives rise to approximately a 4:1 mixture of the *para*- and *ortho*-bromotoluenes (ref. 4). The *para*-selectivity is enhanced in trifluoroacetic acid so that approximately 90 % of the *para*-isomer is produced, but greater selectivity than this is unusual.

Even the use of zeolites has not led to *para*-selectivities of outstanding magnitude (Ref. 5). Sasson's group have shown that one reason for the relatively poor selectivity of bromination of toluene in the presence of a zeolite is the development of a competitive side-reaction in which HBr generated by the reaction catalyses direct bromination outside the pores of the catalyst (ref. 6). The HBr can, of course, also damage the structure of the zeolite. In an attempt to overcome such problems, Sasson's group attempted to scavenge the HBr by addition of propylene oxide (ref. 7). This had the desired effect of putting up the selectivity, to 90 % *para*, but unfortunately the catalyst was deactivated completely at low conversion of the toluene and a significant yield could be obtained only by further additions of fresh catalyst. Therefore, this method does not provide a useful synthetic procedure.

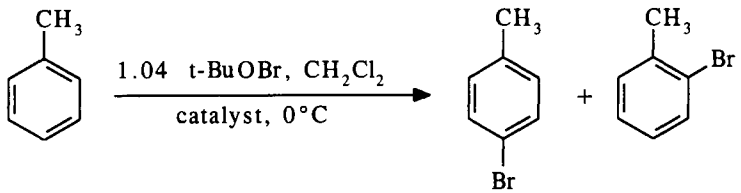
Our own earlier work on the chlorination of toluene had been subject to similar constraints. In this case, chlorination with *tert*-butyl hypochlorite had proved to be advantageous. In the presence of silica gel as catalyst the yield of chlorotoluenes was quantitative but the regioselectivity was more or less statistical (ref. 8). However, the use of proton-exchanged zeolite X allowed the production of chlorotoluenes with a *para*-selectivity of more than 90 % (Fig. 4) (ref. 9). No HCl is generated in this process since the by-product is *tert*-butanol, and there is no inhibition of the catalyst. Indeed, the catalyst can be reused if necessary.



silica	35 %	65 %
zeolite HNaX	91 %	9 %

Fig. 4. Chlorination of toluene over different catalyst

It was of interest to see if the use of *tert*-butyl hypobromite would provide similar opportunities for regioselectivity to those found in the case of chlorination reactions with *tert*-butyl hypochlorite. The initial indications were favourable : use of H zeolite X as catalyst in dichloromethane solution gave an almost quantitative yield of bromotoluenes with a *para* : *ortho* ratio of 81:19 (Fig. 5) (ref. 10).

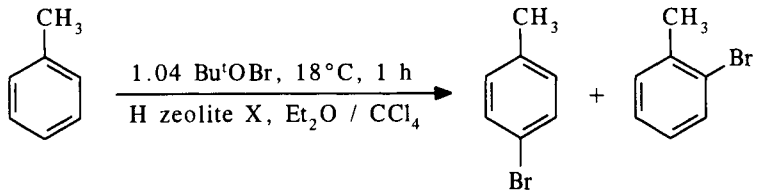


catalyst	yield	proportions
$MeSO_3H$	47 %	46 : 54
synclyst	97 %	52 : 48
H zeolite X	99 %	81 : 19

Fig. 5. Bromination of toluene with *tert*-butyl hypobromite over various catalysts

In our previous studies on chlorination of toluene we had found that solvent had an important effect on the selectivity. In particular, the use of diethyl ether as a co-solvent was advantageous for the production of a high proportion of the *para*-isomer (ref. 9). An experiment in which the amount of ether in a tetrachloromethane/diethyl ether solvent mixture was varied under otherwise identical reaction conditions (1h reaction at 18°C with 1.04 molar equivalent of *tert*-butyl hypobromite) demonstrated that diethyl ether also had a marked influence on the selectivity of the bromination reaction (Fig. 6). There was also an effect on the yield of the reaction as performed under these standard conditions. As the

proportion of ether was increased to around 10 %, the yield of bromotoluenes after a 1h reaction increased, probably reflecting an increase in rate as the polarity of the reaction medium increased. At higher proportions of ether, however, the yield decreased, probably as a result of an increasing tendency to reaction of the *tert*-butyl hypobromite with the diethyl ether present. Therefore, a compromise has to be struck, but it is clear that by use of excess *tert*-butyl hypobromite it is possible to obtain a good yield of *para*-bromotoluene with almost total regioselectivity.



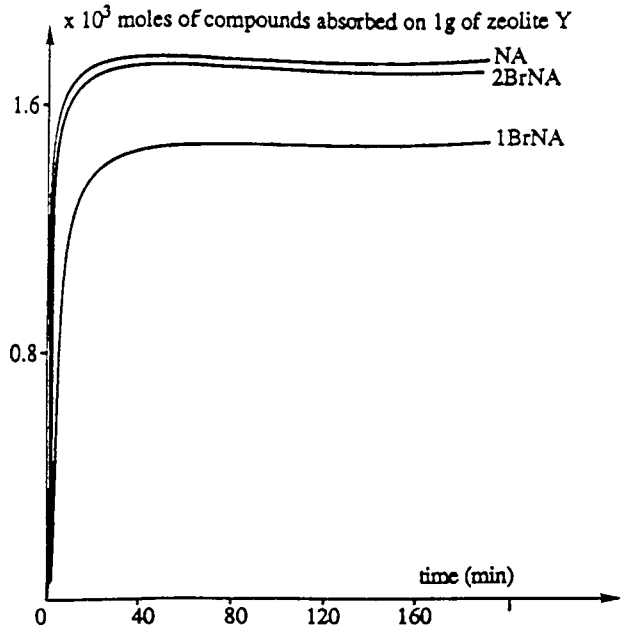
% Et_2O in CCl_4	Yield	Proportions
1	63 %	86 : 14
2.5	72 %	92 : 8
5	75 %	95 : 5
10	76 %	96 : 4
15	71 %	97 : 3
20	70 %	97 : 3
25	64 %	98 : 2
50	59 %	99 : 1
75	49 %	100 : 0

Fig. 6. Effect of diethyl ether on the bromination of toluene

Selective Bromination of Naphtalene

Having solved the problem of selective bromination of toluene, we turned our attention next to an even more difficult problem - the selective production of 2-bromonaphthalene by direct bromination of naphthalene. Traditional bromination of naphthalene produces only around 1 % of the 2-bromo isomer (ref. 4), the production of the 1-bromo isomer being much readier. Studies of the absorption of naphthalene and the isomeric bromonaphthalenes by a range of different zeolites showed that there was a significant difference between the amounts of the two bromonaphthalenes absorbed by zeolites X and Y (e.g. Fig. 7) (ref. 11), although the difference was not as marked as might have been hoped. Nevertheless, this

observation indicated that there may be some possibility of improving the β-selectivity by the use of X or Y type zeolites.



NA = naphthalene
2BrNA = 2-bromonaphthalene
1BrNA = 1-bromonaphthalene

Fig. 7. Absorption of naphthalene derivatives on zeolite Y

This work is in its early stages, but it is already clear that a significant improvement in β-selectivity can be achieved by use of H zeolite Y as the catalyst for the bromination of naphthalene with *tert*-butyl hypobromite (Fig. 8) (ref. 11). It remains to be seen whether further improvements can be achieved by variation of the counterion or by variation of solvent. Such studies are currently in progress.

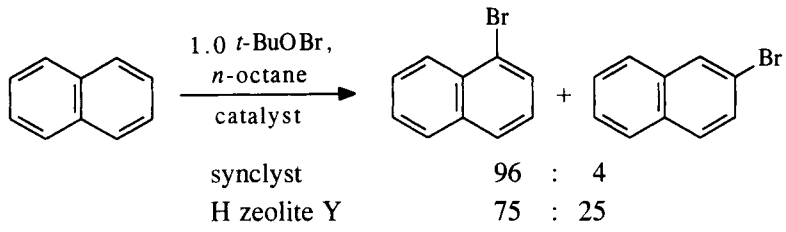
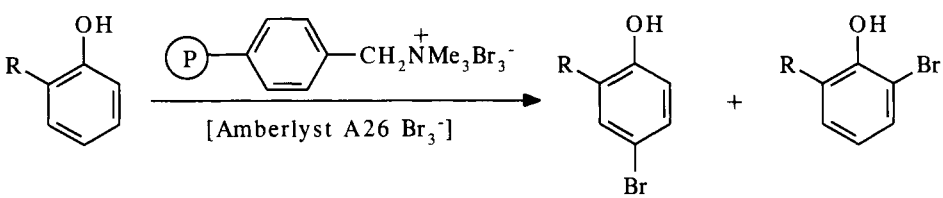


Fig. 8. Bromination of naphthalene over different catalysts

Selective Bromination of Phenols

The selective monobromination of phenols has always proved difficult as a result of the ease of polybromination. Therefore, it has been common practice to use more complex, multi-stage procedures to generate monobromophenols (ref. 12), with all the attendant disadvantages. Our general interest in the development of selective synthetic methods based on the use of solids as catalysts or controlling agents (ref. 13) prompted us to consider the possibility of gaining control over the bromination of phenol by such means. *para*-Bromination of phenols has previously been achieved by use of tetrabutylammonium tribromide in solution (ref. 14). This suggested the possibility of using Amberlyst-A26 tribromide as a solid reagent for convenient *para*-bromination of phenols. Indeed, simply stirring a solution of phenol in dichloromethane with a slight excess of the resin tribromide, in the dark, for 24 hours, resulted in the production of *para*-bromophenol in 86 % yield with only 7 % of the *ortho*-isomer. The reaction could be applied to a range of monosubstituted phenols (Fig. 9) (ref. 15).



R		
H	86 %	7 %
MeO	90 %	7 %
Cl	76 %	20 %
Me	85 %	trace

Fig. 9. Selective *para*-bromination of phenols with Amberlyst-A26 tribromide

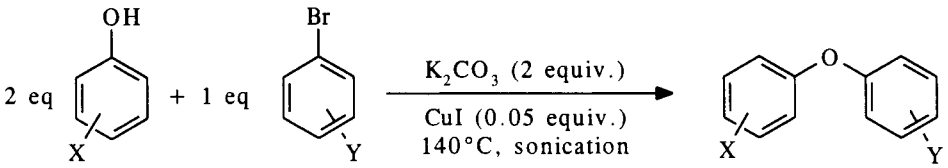
With 3-methylphenol (*meta*-cresol), around 8 % of dibromo products result when one equivalent of brominating agent is used, and this rises to 23 % of dibromo products on attempted monobromination of 3,5-dimethylphenol with 1 molar equivalent of resin. Nevertheless, the good yields of products obtained from the mono-substituted phenols tried demonstrate that this is a powerful new synthetic method for the organic chemist.

For large scale work the cost of the resin might be a major disadvantage unless it could be recovered. We have therefore taken a sample of resin filtered off after a reaction and reconverted it into the tribromide by addition of bromine. Reuse of this resin in a further reaction with phenol gave results which were very comparable with those obtained using the original resin. Therefore, recycling of the resin appears to be a viable possibility.

BROMOAROMATICS IN THE SYNTHESIS OF DIARYL ETHERS

Despite the importance of many substituted examples in the agrochemical and the pharmaceutical industries, methods for the synthesis of diaryl ethers are poor. The most general approach involves the reaction of an alkali metal phenolate with a halogenobenzene in the presence of a catalyst of copper or a copper salt, as developed by Ullmann and co-workers at the turn of the century (ref. 16). However, the reaction requires high temperatures (typically 180-220°C) (ref. 17) and long reaction times (ref. 18) and often produces only moderate yields for substituted examples unless there are electron-withdrawing groups on the halogenobenzene moiety. It was therefore of interest to see if the method could be improved, in particular with bromoaromatics as the substrates.

Many reactions have been shown to benefit from irradiation with ultrasound (ref. 19). We therefore decided to investigate the effect of ultrasound, different catalysts and the presence of solids on Ullmann diaryl ether synthesis. Indeed, sonication of mixtures of a phenol and a bromoaromatic compound, in the absence of solvent and presence of copper (I) iodide as catalyst and potassium carbonate as base, produces good yields of diaryl ethers at relatively low temperatures (Fig. 10) (ref. 20).



X	Y	Time (h)	Yield (%)	Lit. yield (%)
H	2-MeO	2	75	62
H	4-MeO	2	85	70
H	2-Me	3	72	58
H	3-Me	2	97	42
H	4-Me	3	95	67
2-Me	H	4	50	54
3-Me	H	4	89	63
4-Me	H	4	78	55
2-MeO	H	3	62	60
2-MeO	3-Me	4	73	63
2-MeO	2-Me	3	70	
2-MeO	4-MeO	3	67	55
H	1-Naphthyl	2	74	50
3,5-Me_2	H	4	88	

Fig. 10. Synthesis of diaryl ethers under sonication conditions

APPLICATIONS OF BROMOAROMATICS VIA ORGANOMETALLIC REAGENT FORMATION

Highly Hindered Organoboranes

As part of a continuing interest in the applications of organoboranes as synthetic reagents for organic chemistry (ref. 21), we have recently concentrated our attention on the properties of highly hindered organoboron compounds (ref. 22). In this context we became particularly interested in the synthesis of boron compounds containing a 2,4,6-triisopropylphenyl (tripyl, Trip) group. The obvious starting point for the synthesis of such compounds was 2,4,6-triisopropylbromobenzene, which could be reacted with magnesium to form the Grignard reagent, which on subsequent reaction with boron trifluoride etherate gave rise to ditripylfluoroborane (ref. 23). The latter compound could be reduced to ditripylborane (ref. 23) or converted *via* reaction with another organometallic reagent into an alkylditripylborane (Fig. 11) (ref. 24). The rather extreme steric hindrance around

the boron in the alkylditripylboranes renders them stable in air. They can even be recrystallised from hot methanol in the open atmosphere.

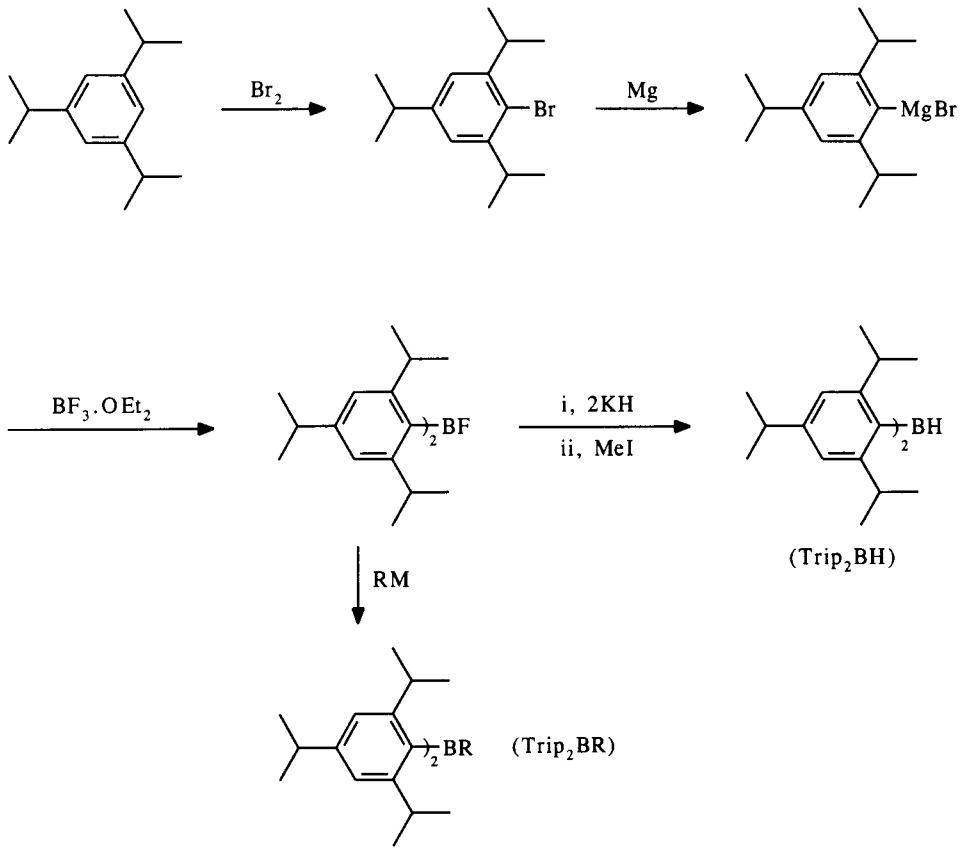


Fig. 11. Synthesis of ditripylboron compounds

The highly hindered ditripylborane is not a good hydroborating agent, reacting readily only with alkynes (ref. 23). It appeared likely, however, that conversion of the alkylditripylboranes into the corresponding borohydrides by reaction with *tert*-butyllithium would provide reducing agents with potential for particularly high stereoselectivity in view of the extreme steric hindrance. This turned out to be the case : ethylditripylhydroborate gave almost 99 % of the less stable *cis*-isomer on reduction of 4-methylcyclohexanone (Fig. 12) (ref. 24). This remarkable stereoselectivity was achieved by reaction at room temperature. Furthermore, the ethylditripylborane by-product of the reaction can easily be recovered and recycled

in view of its stability in air. Therefore, this reagent would appear to have advantages over trisiamylhydroborate, the only previous reagent to have given comparable selectivity, which required reaction at - 78°C and resulted in loss of the boron compound after work-up (ref. 25).

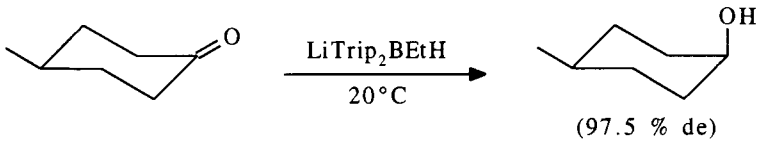


Fig. 12. Stereoselective reduction of 4-methylcyclohexanone

Reaction of tripylmagnesium bromide with trimethoxyborane gives rise to tripyldimethoxyborane, which can be reduced to monotripylborane (Fig. 13) (ref. 26).

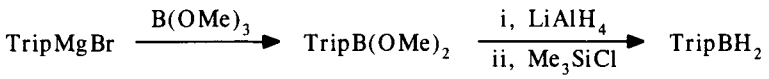


Fig. 13. Synthesis of tripylborane

Tripylborane is an interesting reagent which resembles thexylborane. One of the important uses of thexylborane lies in the synthesis of unsymmetrical thexyldialkylboranes which can then be used in the synthesis of unsymmetrical ketones. However, the reaction is only successful if the alkene used in the first hydroboration step is an internal alkene. Simple terminal alkenes such as 1-hexene react too rapidly with the initially formed thexylmonoalkylborane to allow the reaction to be stopped at that stage. Therefore, mixtures of products result (ref. 27).

By contrast, tripylborane, which is somewhat more hindered than thexylborane, reacts cleanly and highly regioselectively with 1 equivalent of even a terminal alkene to give the corresponding tripylmonoalkylborane. Subsequent reaction with a different alkene gives the corresponding tripyldialkylborane (ref. 28), which can be cleanly converted into the unsymmetrical ketone *via* the cyanoborate reaction (Fig. 14) (ref. 29).

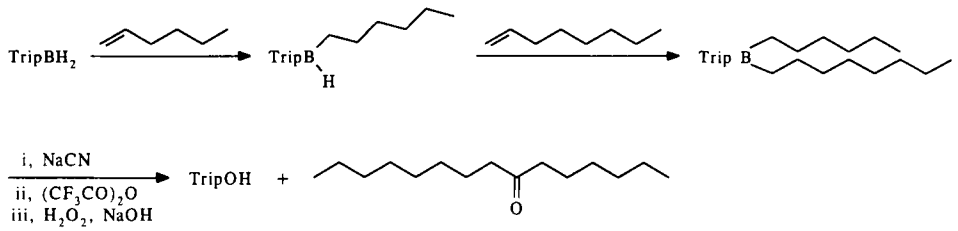


Fig. 14. Synthesis of an unsymmetrical ketone *via* tripylborane

Dialkyltripylboranes have a further advantage over thexyldialkyboranes. Because the group attached to boron is aromatic rather than aliphatic, and because it is electronically activated by the presence of alkyl groups, it is susceptible to attack by electrophiles such as bromine. This process allows ready selective cleavage of the tripyl group from the organoborane to leave an unsymmetrical dialkylboron compound, which can then be reacted with a further organic unit to produce a totally unsymmetrical organoborane even with three primary alkyl groups (Fig. 15) (ref. 28). Such organoboranes have hitherto been available only by circuitous routes (ref. 21). As well as providing an easy access to totally unsymmetrical tri-*primary*-alkylboranes the bromination reaction also gives back tripyl bromide which can be recycled to form more tripylborane.

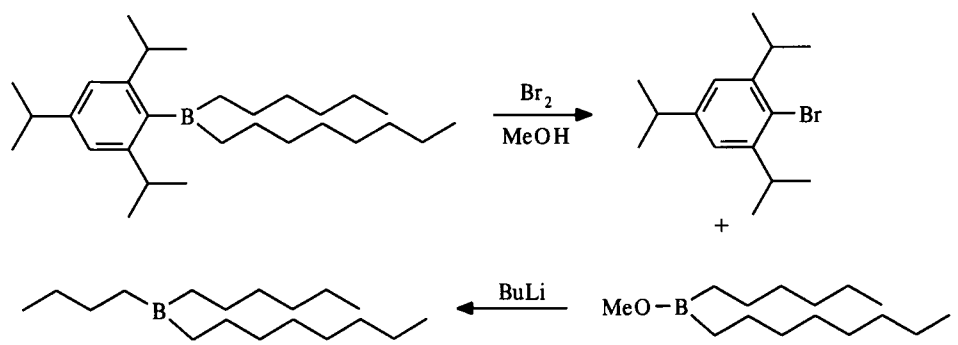


Fig. 15. Synthesis of a totally unsymmetrical tri-*primary*-alkylborane

Intramolecular Trapping of Acyllithiums

We recently demonstrated that organolithium reagents formed by directed metallation of pivaloylanilines would react rapidly with carbon monoxide at 0°C or room temperature to form high yields of dioxindoles (Fig. 16) (ref. 30). This

reaction offers considerable potential for the synthesis of indole derivatives and because it involves the incorporation of carbon monoxide it is potentially applicable to the incorporation of carbon-11 *via* the use of ^{11}CO, which would render the products as potentially useful for medical diagnosis using positron emission tomography (PET). It is known that dioxindoles can be reduced to indoles, but for the reaction to be useful it would be necessary to be able to substitute the benzenoid rings with other groups and it would also be necessary to have the option of alternative substituents at the 3-position. There is no problem with producing products substituted in the benzenoid ring since there is a range of substituted anilines which can be used in the initial reaction (ref. 30). However, the variation of the substituent at the 3-position presents more of a problem. It requires the use of an alternative group for directed lithiation, followed by cyclisation after carbon monoxide uptake. We have therefore attempted to address this problem.

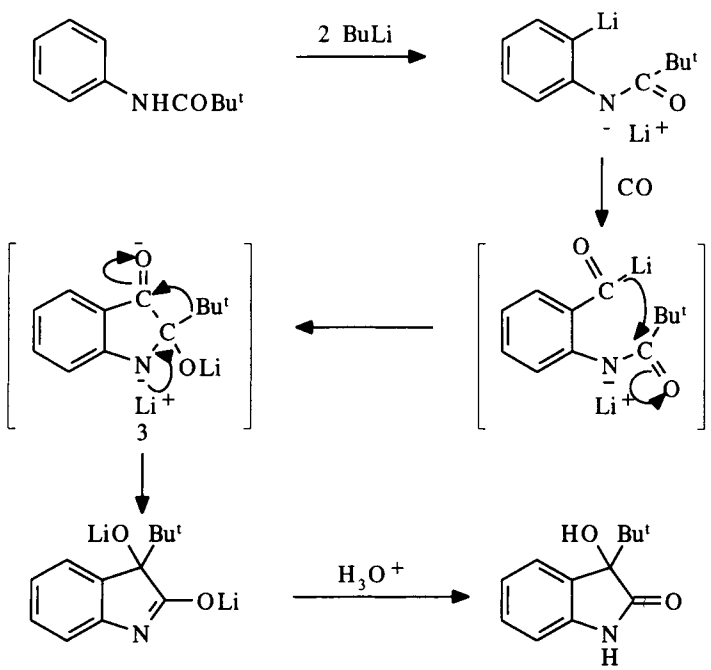


Fig. 16. Formation of 3-*tert*-butyldioxindole *via* lithiated *N*-pivaloylaniline

One group which could have utility in this context is the thiourea group (Fig. 17). Unfortunately, repeated attempts to generate the dianion *via* directed lithiation of *N,*-dimethyl-*N'*-phenylthiourea were unsuccessful. Again, bromo compounds came to the rescue. The 2-bromo derivative could be deprotonated (N-

H), followed by bromine-lithium exchange using 2 equivalents of *tert*-butyllithium to give the desired intermediate. This intermediate readily picked up carbon monoxide and work-up of the reaction mixture gave indigo (Fig. 17) (ref. 31).

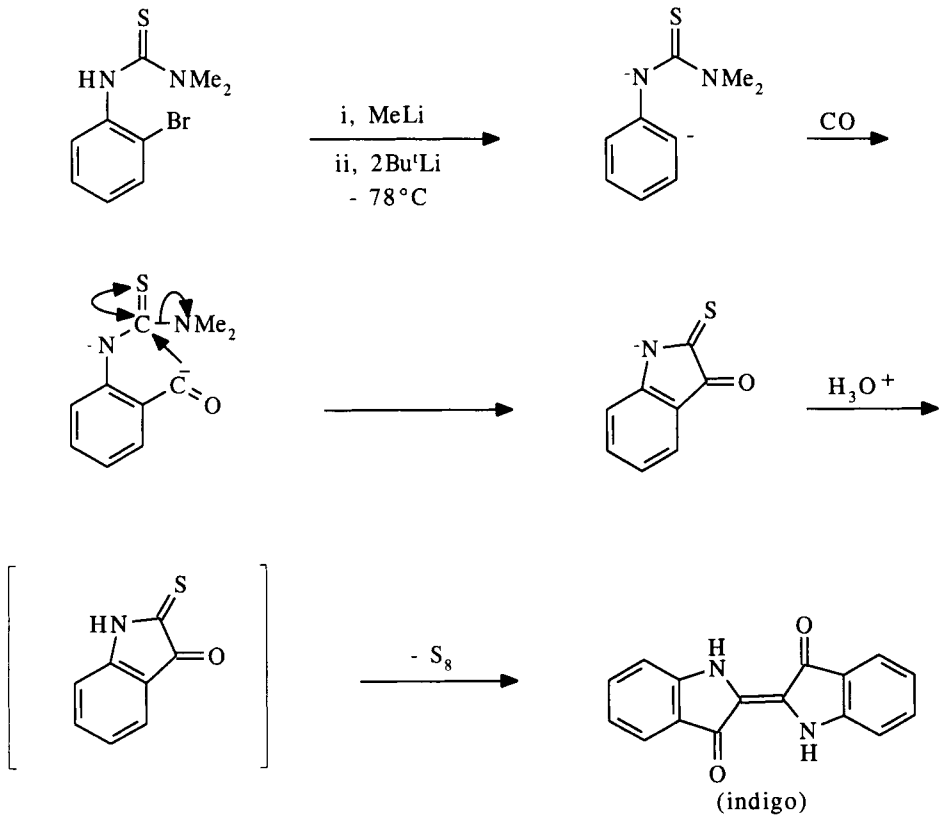


Fig. 17. Production of indigo from 2-bromophenyldimethylthiourea

At the present time we have not attempted to isolate α-thioisatin, the presumed intermediate in the synthesis of indigo. However, it is immediately apparent that if this intermediate could be isolated or intercepted *in situ*, then many possibilities would open up for the conversion of this compound directly into other indole derivatives. It is also apparent that it should be possible to carry out the reaction with substituted thioureas. We shall be exploring these possibilities.

CONCLUSION

Bromo compounds are useful intermediates for the synthesis of a range of more complicated organic compounds *via* direct substitution or by prior conversion into organometallic reagents. They therefore hold a key position in the synthesis of fine chemicals. This position demands that more selective methods for the synthesis of bromo compounds also be developed. In this report we have illustrated the development of selected syntheses of bromoaromatic compounds and demonstrated new ways in which they can be applied in synthetic procedures.

ACKNOWLEDGEMENTS

The work reported in this article was carried out by an able group of students and postdoctoral fellows and in collaboration with industrial colleagues. In particular, Mark Hammond in collaboration with Dr David Walker of BP; Martin James and Ian Matthews in collaboration with Dr Martin Bye of Amersham International; Dr Laurence Vivier, European Community Fellow; Dennis Jones in collaboration with Dr Derek Bassett of Associated Octel; Zhao Jin in collaboration with Professor Andrew Pelter of this department; Gareth Pritchard and Dr. A.P. Shukla, British Council / University of Wales Fellow; made significant contributions. I thank them all, and also the companies involved who, along with the S.E.R.C., The British Council and The University of Wales, provided funding for the research. Finally, I am grateful to Professor Yoel Sasson and the organisers of *Orgabrom'93* for the invitation to present this work in Jerusalem.

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HIGH TEMPERATURE BROMINATION IV[ref. 1]. BROMINATION OF BENZONORBORNADIENE AND BENZOBARRELENE

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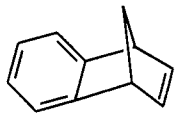
ABSTRACT

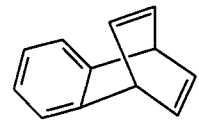
The electrophilic addition of bromine to benzonorbornadiene at 10°C led in high yield to the formation of exo-5-anti-7-dibromide **3**. However, high temperature bromination in decalin at 150°C resulted in the formation of four products **3-6** consisting of nonrearranged and rearranged products in a ratio of 9:1. Conducting the bromination reaction in the presence of free radical inhibitors like 2,4,6-tri-*tert*-butylphenol suppressed the formation of the nonrearranged products. This very strongly supports the assumption that there is a competition between radical and ionic reactions.

Bromination of benzobarrelene in chloroform at 10°C followed by repeated chromatography combined with fractional crystallization allowed us to isolate ten product **10-19**. Structural determination of these compounds revealed that the barrelene skeleton was completely rearranged. **16-19** are alcohol compounds which arise from hydrolysis of **10**, **11**, **13**, and **14**. High temperature bromination of benzobarrelene in decalin at 150°C followed by repeated chromatography combined with fractional crystallization gave us 18 products. Nonrearranged products **22**, **23**, and **24** have been isolated in 50 % yield. All compounds have been characterized properly, especially by 200 MHz ^{1}H NMR and 50 MHz ^{13}C NMR spectra. Furthermore, it has been concluded that high temperature bromination of bicyclic systems gives more nonrearranged products. If the molecule is more strained, the tendency to rearrange decreases as in the case of benzonorbornadiene.

In connection with our continuing interest in the temperature bromination reactions (ref. 2) we have been interested in the bromination reactions of benzonorbornadiene **1** and benzobarrelene **2**.

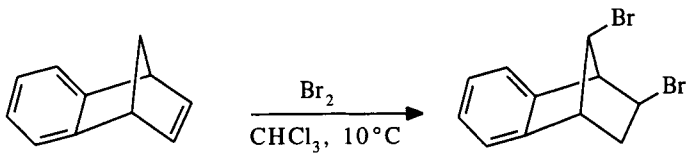


Benzonorbornadiene **1**



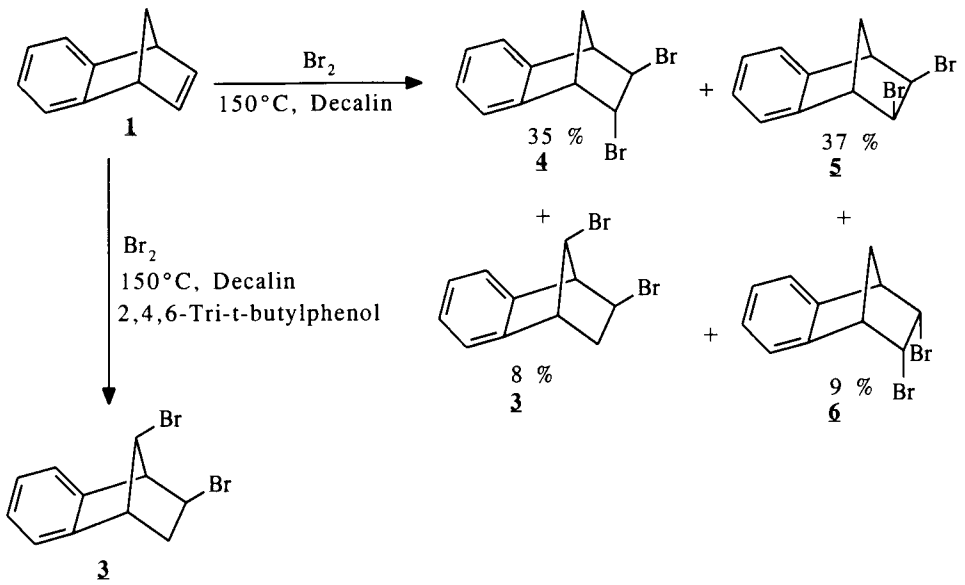
Benzobarrelene **2**

The electrophilic addition of bromine to benzonorbornadiene was first reported by Wittig and Knauss to yield a dibromide (ref. 3). At about the same time, the related addition of bromine to a diacetoxy derivative (substituted in the benzene ring) of **1**, which proceeded with rearrangement, was described (ref. 4).



1 **3** (1)

Addition of bromine to **1** in chloroform solution at 10°C led in high yield to the formation of the exo-5-*anti*-7-dibromide **3**. No other products were isolated. The formation of this rearranged product can be explained in terms of Wagner-Meerwein rearrangement where migration of the aryl group is involved (eqn. 1).



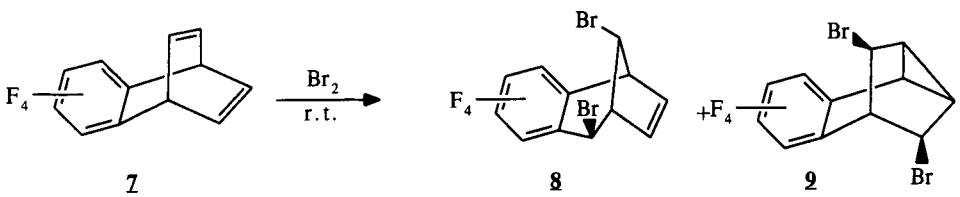
Scheme 1. Influence of free radical inhibitor on the formation of products.

Wilt and Chenier (ref. 5) have studied radical addition of bromine to **1** by taking 1,2-dibromotetrachloroethane, an interesting bromine carrier, to brominate the allylic position. This reagent would also add bromine to the double bond of an olefin. Indeed, quantitative addition of bromine to **1** via this reagent in carbon tetrachloride during irradiation with a sun lamp and under reflux gave *trans*-2,3-dibromobenzo-norbornene **4** and exo-*cis*-2,3-dibromobenzonorbornene **5** in a ratio of 89 : 11. No rearranged product **3** was isolated.

In the course of studying the bromination reactions of the bicyclic systems we noticed that the reaction temperature has a dramatic influence on the product distribution. Increasing of the temperature gives non-rearranged reaction products (refs. 1,2). For this reason, we submitted **1** to high temperature bromination. To a solution of **1** in decalin at 150°C was added a hot solution of bromine in decalin in one portion. The colour of bromine disappeared immediately. After silica gel chromatography followed by fractional crystallization we isolated four products **3-6** in yields 8, 35, 37, and 9 % respectively. The structure of these compounds has been elucidated on the basis of spectral data by ^{1}H NMR and ^{13}C NMR experiments and by comparison with those reported in the literature. Symmetrical endo-*cis*-isomer **6** has been observed for the first time. Studies concerning the mechanism of syn-addition show that the syn-adduct can arise either from direct

syn-collapse of an ion pair or from rotation followed by anti-collapse (ref. 6). Because of the rigid skeleton in **1**, a bond rotation is out of the question. In this case we assume that the high temperature bromination is occurring by a free radical mechanism. Radical intermediates are much less likely to rearrange. This could explain also our stereochemical results. Conducting the bromination reaction in the presence of free radical inhibitors like 2,4,6-tri-tert-butylphenol suppressed the formation of the nonrearranged products. This very strongly supports the assumption that there is a competition between radical and ionic reactions.

In the second part of this work we studied the bromination of benzobarrelene at room temperature and at 150°C. Some dipolar addition reactions to the benzobarrelene have been reported by Paquette and al (ref. 7). Surprisingly, there is no report in the literature on bromination of benzobarrelene. However, Barkash and al. (ref. 8) has reported bromination of tetrafluorobenzobarrelene **7** and isolated from complex reaction mixture only compounds **8** and **9** (Scheme 2).



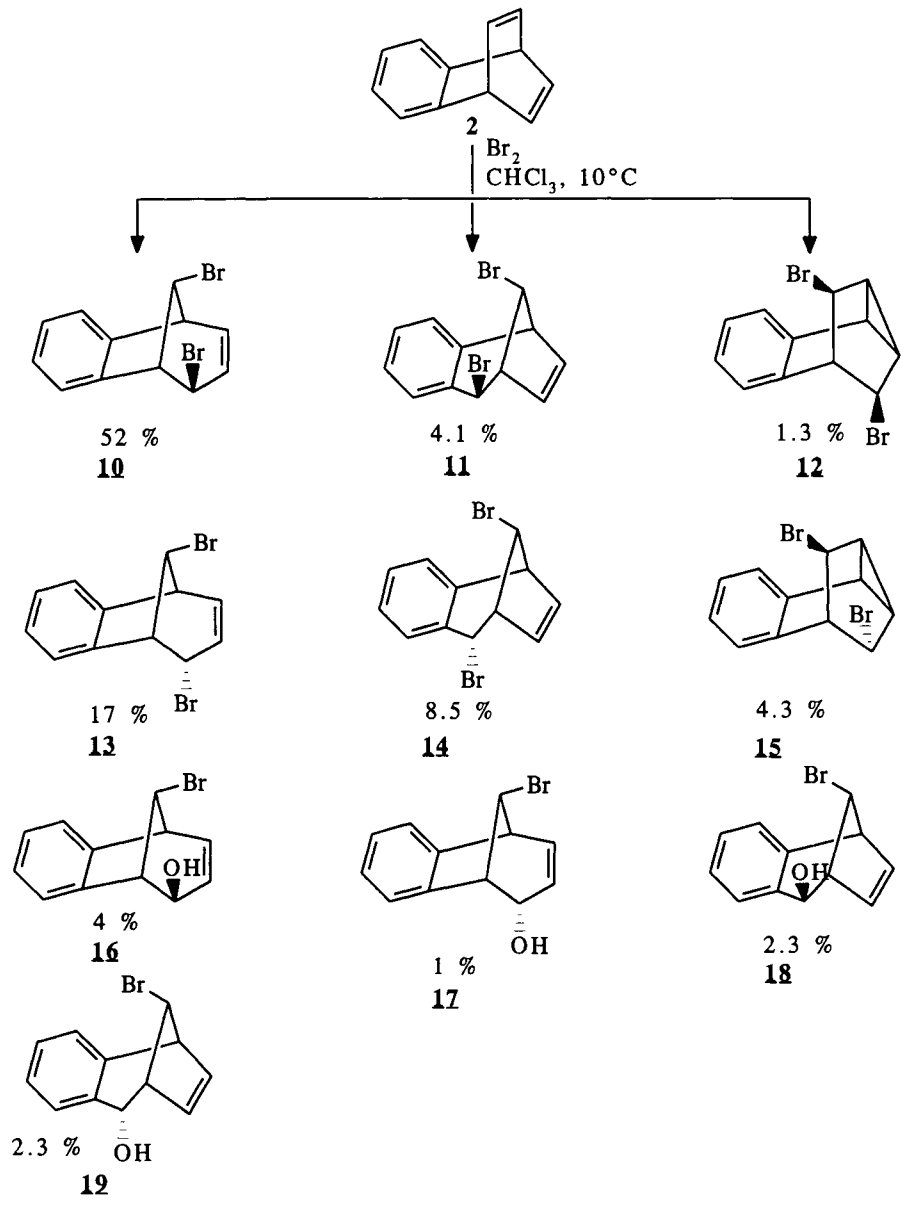
7 **8** **9**

Scheme 2. Bromination of tetra fluorobenzobarrelene at room temperature

We reacted **2** first with bromine in chloroform at 10°C. ^{1}H NMR studies have revealed that the reaction mixture was very complex and consisted of six products. This mixture was submitted to silica gel column chromatography. Careful repeated chromatography followed by fractional crystallization allowed us to isolate ten products (Scheme 3). IR analysis indicated that a hydroxyl group was incorporated in compounds **16-19**. Therefore, we assume that these products have been formed by partial hydrolysis of compounds **10-14**. Structural determination of compounds **10-19** revealed that the barrelene skeleton was rearranged completely.

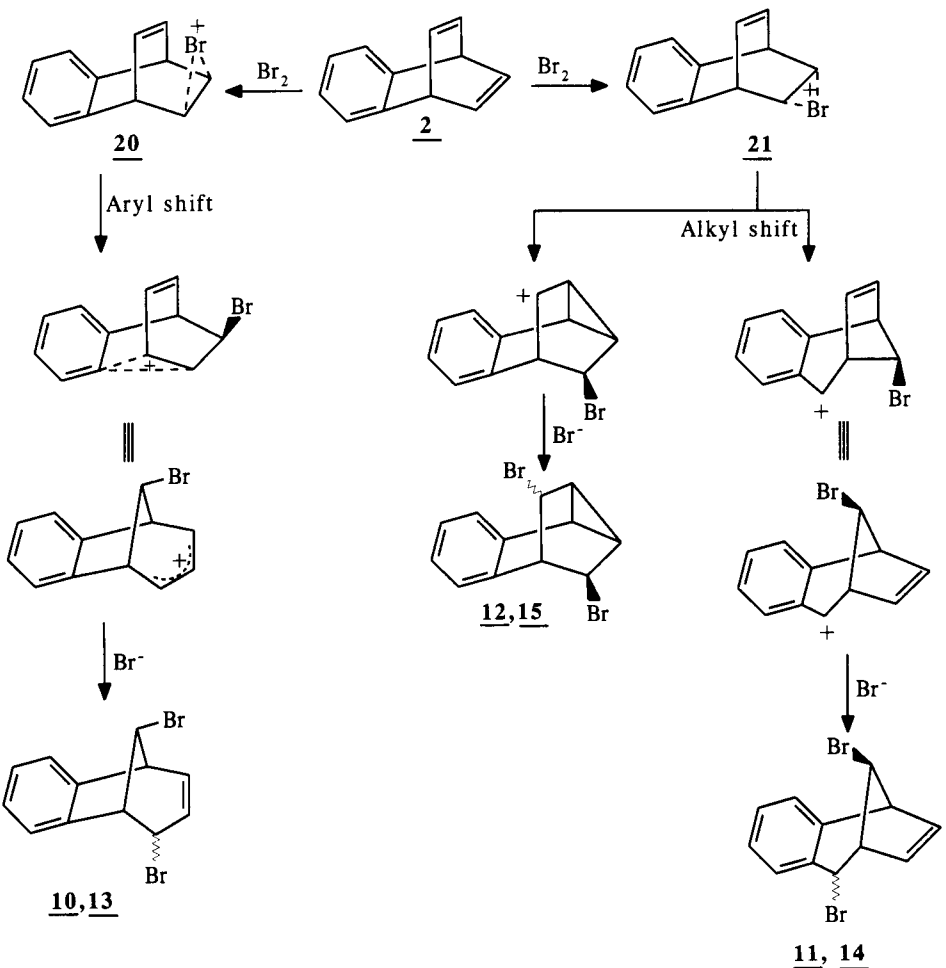
For the formation of the rearranged products we propose following reaction mechanism. Generally, a positive charge when placed on the double bond of **2** induces a Wagner - Meerwein rearrangement and transforms the [2.2.2] ring system into the [3.2.1] ring system which then reacts with bromide ion to give the products. It is evident from the bromine configuration at bridge carbon in major products **10** and **13** that initial attack by the bromine has occurred from exo-face of

the π-system (Scheme 4). Most reasonably, the driving force of this mode of addition is supplied by the formation of aryl bridged intermediates.

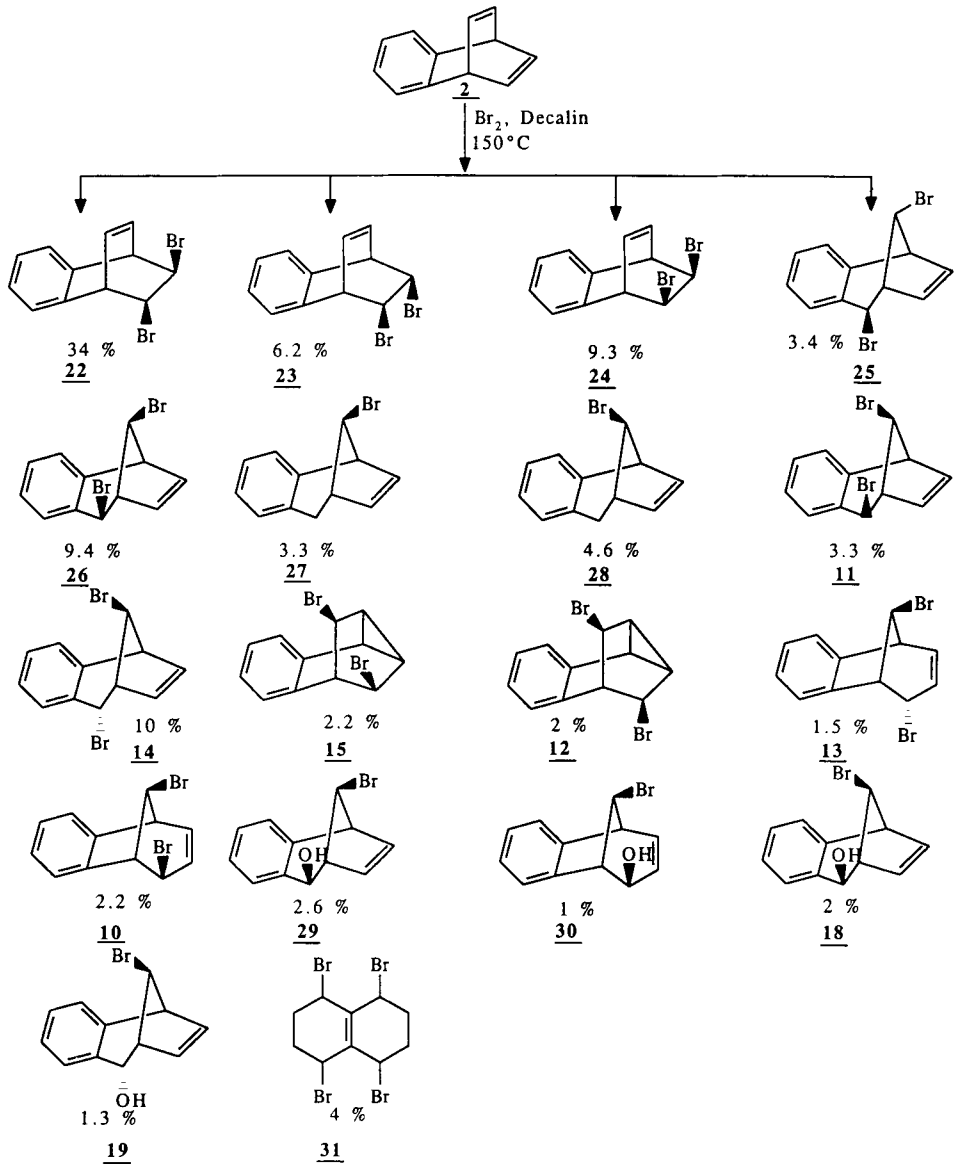


Scheme 3. Products in the bromination of benzobarrelene in $CHCl_3$ at 10°C.

The formation of alkyl shifted products **11** and **14** can be explained in terms of the formation of endo-intermediate **21** formed by endo attack of bromine to **2** (Scheme 4). The determined endo-configuration of the bromine atom at the bridge carbon is also in agreement with endo-attack. Endo-Intermediate **21** is probably also responsible for the formation of cyclopropane products **12** and **15**. The existence of cyclopropane ring in **12** and **15** has been determined by ^{1}H and ^{13}C NMR chemical shifts and especially by analysis of cyclopropane J_{13CH} coupling constants (168 and 181 Hz). On the basis of the symmetry in the molecule **12** we have distinguished easily between isomers **12** and **15**. Aryl and alkyl shift products **10**, **11**, **13**, and **14** contain benzylic and allylic bromine atoms which can be hydrolized easily on column material.



Scheme 4. Mechanism of formation of products in the bromination of benzobarrelene.

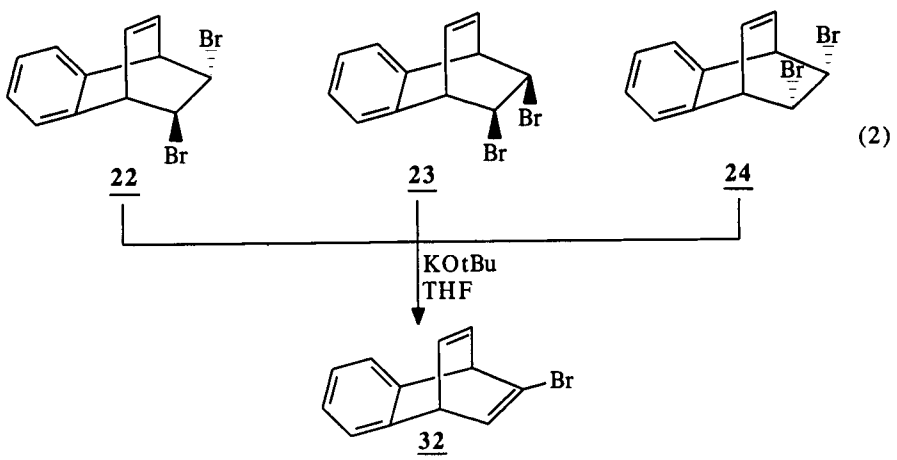


Scheme 5. Products in the bromination of benzobarrelene in decalin at 150°C

Therefore, we isolated for additional products **16-19** which arise from hydrolysis of **10**, **11**, **13**, and **14**. There was no hydrolysis product derived from cyclopropane compounds as expected.

Next we studied high temperature bromination of benzobarrelene at 150°C. NMR analysis indicated that the reaction mixture was very complex and consisted of at least ten products. After repeated column chromatography combined with fractional crystallization we have been able to separate 18 compounds (Scheme 6). Four of them were bromoalcohol compounds **18**, **19**, **29** and **30**. After high temperature bromination we expected three isomeric non-rearranged products with benzobarrelene skeleton and isolated **22**, **23**, and **24** in yields of 34, 9.3, and 6.2 %, respectively. Because of the very close structural similarity we were not able to make a clear-cut differentiation between the stereochemistry of **23** and **24**. Therefore, we carried out an X-ray analysis (ref. 9) of the isomer **23**.

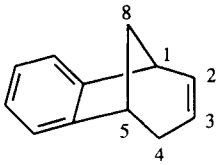
Treatment either of pure isomers or of a mixture consisting of **22-24** with potassium-tert-butoxide provided **32** in high yield (eqn. 2).



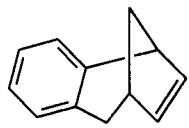
(2)

Structural assignments of all isolated compounds were based mainly on the proton coupling constants which exhibited the correct configuration for these closely related benzobicyclo[3.2.1]octadienes. Those coupling patterns which are important for stereochemical characterization are J_{45}, J_{18}, and J_{58}. As a consequence of the rigid geometries and reliability of the Karplus rule in bicyclo[3.2.1]octane systems, the dihedral relationship of the C-H-5 (C,1-H) bond to an endo (20°) or to an exo-proton (80°) are sufficiently distinctive to be releaved by magnitude of the spin-spin interaction. Thus, the high value of J_{18} and J_{58} is uniquely accomodated by the endo-orientation of bromine. The configuration of the bromine at C_4 was also determined from the coupling constant J_{45}. We observe a large coupling constant J = 4-5 Hz in the case of an endo-orientation of bromine and a small coupling J = 1.5-2.5 Hz for an exo-orientation. Among the products, we see two different

bicyclo[3.2.1]octene systems X and Y. which can be easily distinguished on the pattern of aromatic and olefinic resonances.

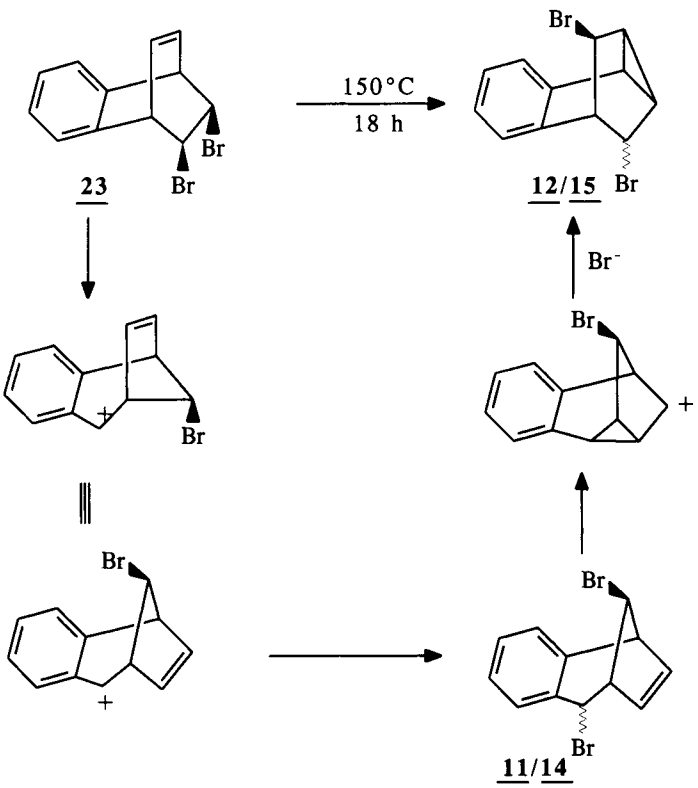


X

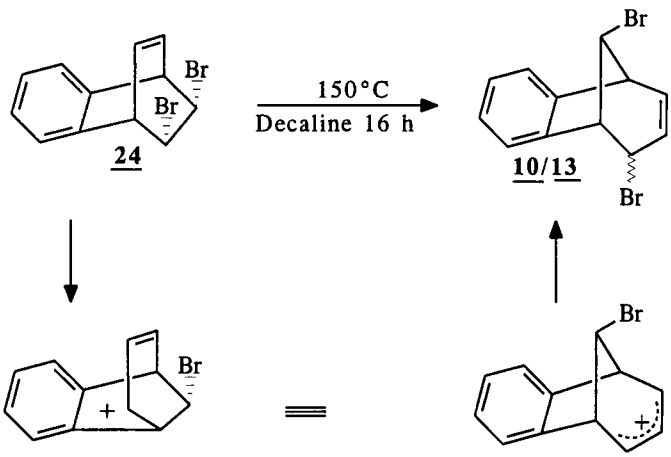


Y

The ratio of nonrearranged products to rearranged products produced during this high temperature bromination was 1:1. In the high temperature bromination of benzonorbordaniene we obtained a value of 9:1 for this ratio. In order to test whether the rearranged products are primary or secondary products, we reacted them under the given reaction conditions and observed that products **22-24** are stable. However, prolonged heating (18 h) of **23** resulted in the formation of **12/15** where **11/14** were the presumed intermediates.



Scheme 6. Mechanism of rearrangement of **23**

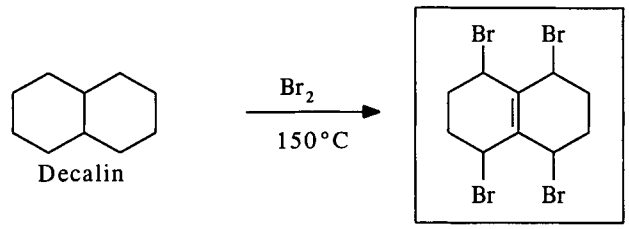


Scheme 7. Mechanism of rearrangement of **24**

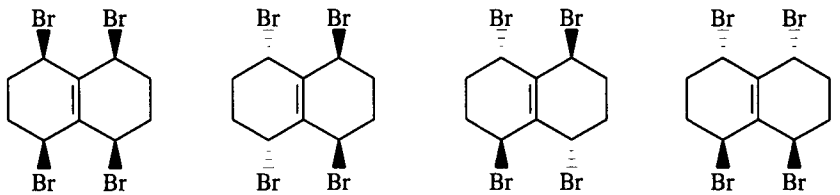
On the other hand, isomeric **24** rearranged under the same reaction conditions (150°C, 16 h) to the isomeric [3.2.1] systems **10/13** (Scheme 7). On the basis of these results we assume that the rearranged products are primary products.

From the high temperature reaction mixture we also isolated Wagner-Meerwein rearranged products arising from aryl and alkyl shifts. Surprisingly, we encountered two HBr-addition products **27** and **28** in 4.5 and 3.3 %. We believed at first that these products have been formed by HBr-addition to **2**. However, treatment of **2** with HBr did not provide **27** and **28**. For the formation mechanism for these compounds, we assume that bromine radical firstly add to double bond of benzobarrelene **2** and then rearranges to stable benzyl radical, which can abstract a hydrogen atom from solvent molecule to give **27** and **28**.

Lastly, we isolated a tetrabromo compound **31** (ref. 10) which is derived from solvent. ^{1}H and ^{13}C NMR spectra of **31** indicates the formation of a highly symmetrical compound whose configuration is not known. Possible configurations are given on scheme 10. On an independent reaction we treated decalin with bromine at high temperature and obtained **31** in high yield.



(3)



Finally, we would like to conclude that high temperature bromination of bicyclic systems gives more non-rearranged products. If the molecule is more strained, the tendency to rearrange decreases as in the case of benzonorbornadiene. On the other hand, substituents at double bond of benzobarrelene retards also rearrangement (ref. 1).

Acknowledgements

The authors are indebted to the Department of Chemistry and Atatürk University for financial support (Grant Nr. 1991/6, Arastirma Fonu) of this work and State Planning Organization of Turkey (DPT) for purchasing a 200 MHz NMR.

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BROMINATION OF ERGOLENE AND ERGOLINE STRUCTURES - NEW RESULTS

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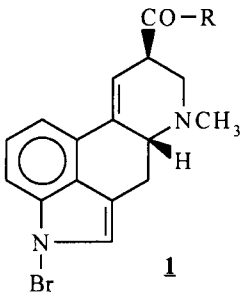
SUMMARY

The technical aspect of 2-bromo-α-ergocryptine synthesis, including the characterisation and significance of the impurities obtained in the production process, were reviewed. In the continuation new ergolene and ergoline compounds were synthesized and tested for the pharmacological activity.

INTRODUCTION

The preparation of halogeno-compounds of lysergic acid, isolysergic acid and their derivatives, e.g. esters, amides and ergot alkaloids, was already presented in the year 1948 by Sandoz (ref. 1). For this purpose N-bromo-compounds like N-bromosuccinimide, N-bromoacetamide, N-bromophthalimide and others were used as the brominating agents. The entrance of bromine atom onto indole nitrogen (position 1) was presumed. A series of bromo-derivatives **1** has been prepared. Later investigations (refs. 2, 8) of the same research group, however, led to the correction of these results : the substitution was actually on the position 2 in indole nitrogen. Among the synthesized 2-bromo derivates of ergot alkaloids the pharmacologically very active compound was selected : 2-bromo-α-ergocryptine **2**. It has proven therapeutically useful for an efficient inhibition of prolactine secretion (ref. 4), Parkinson's disease (ref. 5), acromegalia (ref. 6) and for the treatment of some diseases associated with serum prolactine level (ref. 7). Recently, a surprisingly good activity against gastrointestinal ulcers has been found (refs. 8,9) and beneficial effects on healing of bone fractures have been observed (ref. 10).



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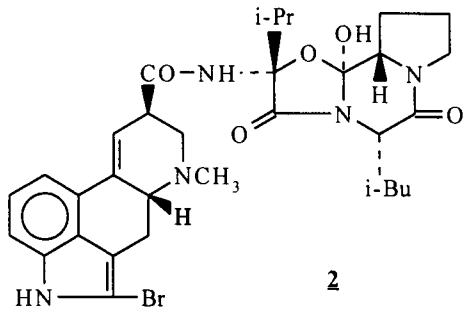
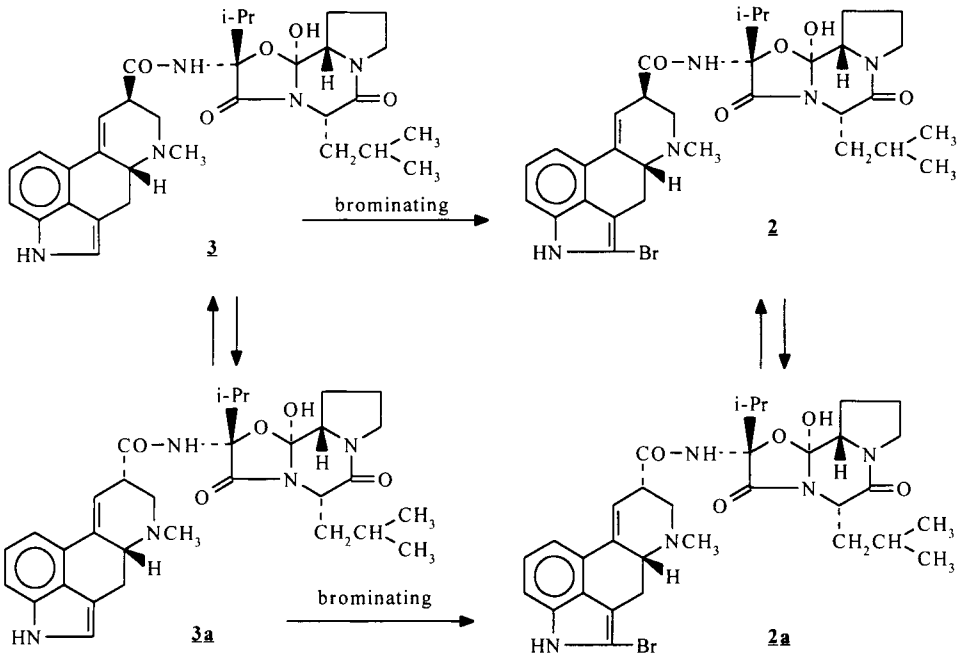


2

Today, 2-bromo-α-ergocryptine (bromocriptine) is the second (after dihydroergotoxine) most extensively used compound from the group of ergot alkaloids.

CHEMISTRY

In general, the introduction of bromine in ergolene or ergoline structure results in remarkable change in pharmacological activity of the parent compounds. After intensive research work of several research groups many useful methods for 2-bromination have been developed. Practically, all methods are accompanied with many side reactions. Therefore, the best attainable yields of product **2** are in the range of 60 - 70 % of the theory :



Scheme 1. Bromination of ergolene

Table 1 shows the comparison between the known methods, applied to the model of bromocriptine **2**. The yields of reproduction experiments are cited in parentheses. This data show a remarkable higher yield (between 60 and 65 %) using NBS but, as expected no reaction with DMSO/HBr reagent. For industrial production only the methods using the reagents : NBS, PHT and HBr/Br_2 (in dichloromethane) are of great practical value. Introduction of bromine using these reagents is a radical type reaction. It is also necessary to use either the solvents containing traces of peroxides or hydroperoxides, or radical initiating compound like : benzoylperoxide, 2,2'-azobis-(2-methylpropionitrile)-AIBN, can be added to start the reaction. Bromocriptine **2** is now produced in industrial scale using natural ergot alkaloid α-ergocryptine **3** as a raw material. However, in recent years, α-ergocryptine is obtained by large scale fermentation procedure.

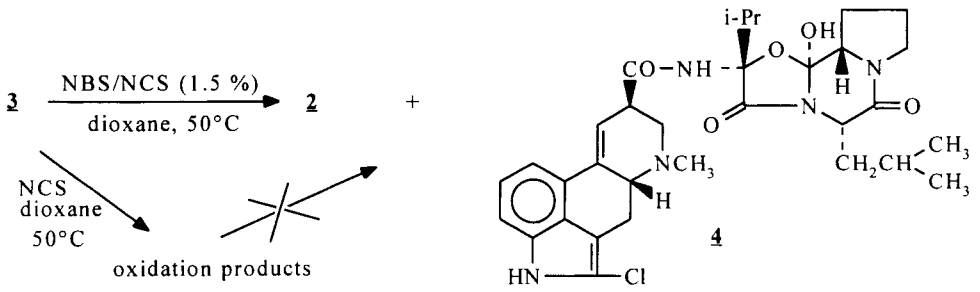
Table I. Comparison of brominating methods of preparation of bromocriptine **2**

Brominating agent	Reaction condition	Yield of **2** (reproduction)	Reference
N-Bromosuccinimide, NBS	dioxane 60°C, 70 min.	38.4 % (60 - 65 %)	(ref. 14)
N-Bromocaprolactam	dioxane 20°C, 6 hours	75 %	(ref. 12)
N-Bromophtalimide	dioxane 20°C, 6 hours	60 %	(ref. 12)
Bromine.dioxane complex	dioxane 20°C, 4 hours	57 %	(ref. 12)
Pyrrolidone (2)-hydrtribromide PHT	dioxane 50°C, 30 min. AIBN	62.2 %	(ref. 15)
1,3-Dibromo-5,5-dimethyl-hydantoin (Dibromantine)	dioxane 40°C, 60 min. AIBN	62.2 %	(ref. 16)
HBr / Br_2	dichloromethane 0°C, 2 hours	73.5 %	(ref. 17)
Piperidone (2)-hydrotribromide	dioxane 20°C, 2 min.	78.2 %	(ref. 28)
3-Bromo-6-chloro-2-methyl-imidazo-(1,2b)-pyridazine-bromine complex	dichloromethane 20°C, 2 min.	75 % (40 %)	(refs. 13,31)
DMSO/HBr	DMSO 20°C, 15 min.	74 % (0 %)	(ref. 18)
Quinoline, Br_2 complex	dichloromethane 20°C, 10 min.	41 %	(ref. 19)

The quality of the product must meet high requirements of USP XXII and FDA regulations, considering high pharmacological activity of any present impurities. Therefore, the investigation of impurities and degradation products has absolutely been necessary.

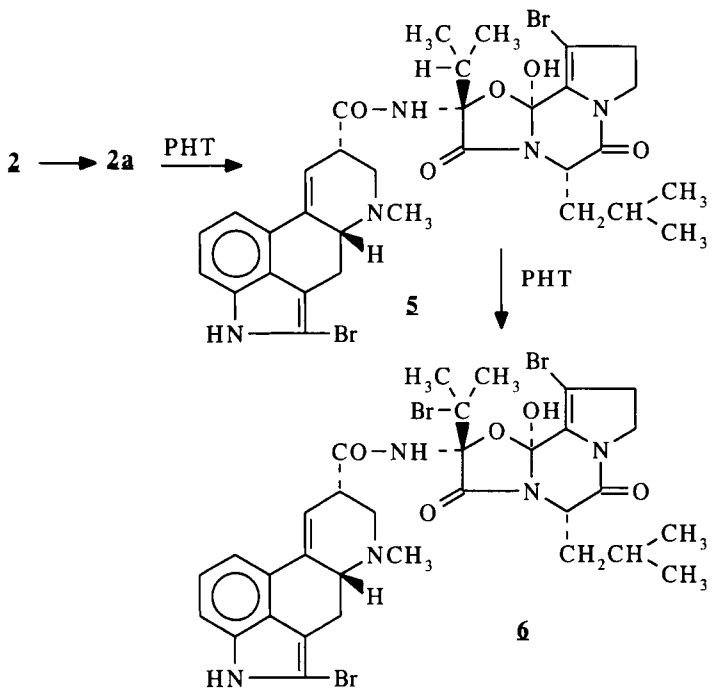
The well know isomerisation (ref. 11) at the position 8 in ergolene nucleus is usually easy and is difficult to be totally avoided. The moderate acidic media, lowering of temperature and non-polar solvents can successfully suppress this reaction. At any case, the iso compound : 2-bromo-α-ergocryptinine **2a** can readily be transformed back into bromocriptine **2**, also in industrial scale.

Bromination of α-ergocriptine **3** with commercial N-bromosuccinimide (NBS) can lead to the formation of traces of a mysterious by-product, finally identified as 2-chloro-α-ergocryptine **4**. Investigation of NBS indicated that it contains up to 1.5 % of chlorine (probably as N-chloro-succinimide, NCS). This chlorination occurs only in the presence of NBS, never with NCS alone :



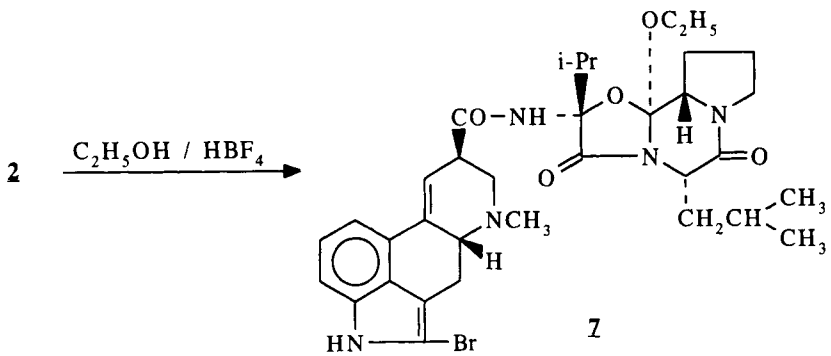
It seems that NCS should be involved in free radical reaction generated by NBS. But, the presence of traces of **4** also indicative of the production method unless extremely pure NBS has been used for bromination. Instantly, for the regular preparation of **4** the method with N,2,6-trichloro-4-nitroacetanilide is more successful (ref. 2).

Bromination of **3** with pyrrolidone-(2)-hydrotribromide (PHT) does not produce any traces of compound **4**, even in the presence of chloride ion, however other side reaction can be observed. Just a small excess of PHT produces the higher brominated compounds **5** and **6** :



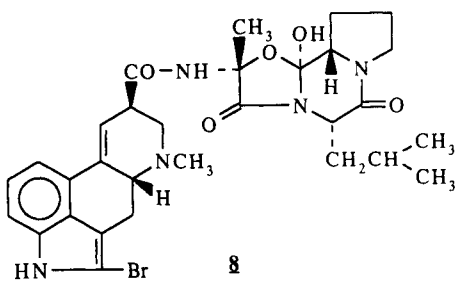
In the first step bromocriptine **2** is isomerized to **2a**, followed by an attack on proline ring in aminocyclol moiety of the molecule (formation of a new double bound on 10'-11', and bromination). This dibromo-compound **5** is brominated additionally on C-2'-propyl group. Tribromo-compound **6** is very lipophilic and practically devoid of pharmacological activity. Hydroxy group and amide groups remain intact after all these reactions.

Transformation of bromocriptine free base **2** into water soluble salt -mesylate, is the only way to obtain a suitable therapeutical form. Crystallization of mesylate using alcohol as a solvent in the presence of excess of strong acid, e.g. methanesulphonic acid can induce formation of 12'-0-alkyl-derivative 7. Until now this derivatisation of ergot molecule has been practically unknown. In continuation we developed the preparative method for obtaining these compounds, (using tetrafluoroboric acid as a catalyst) (ref. 20).



7

Among the series of ergot alkaloids the derivatives of α-ergosine were exhaustively investigated by our group. 2-Bromo-α-ergosine **8** and 2-bromo-9,10-dihydro-α-ergosine **9** were synthesized using the methods with PHT (ref. 15) or with polymeric bonded bromine **18**, **19** or **20**.



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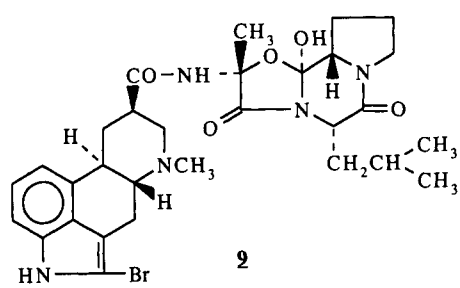

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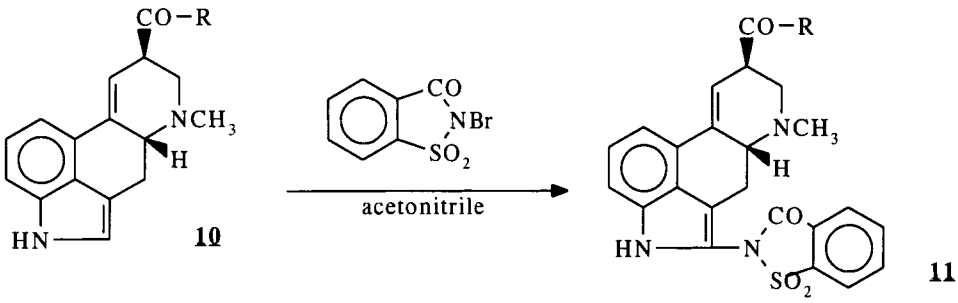
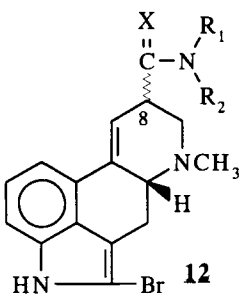
2-Bromo-α-ergosine **8** has remarkable activity on arterial hypertension, migraine and heart arrhythmias (refs. 21,22). The action of 2-bromo-9, 10-dihydro-α-ergosine **9** on heart arrhythmias is of a very long duration and of great stability (refs. 23, 24).

Surprisingly, the bromination of ergoline structures with N-bromosaccharin yielded as the main product the ergoline derivatives with a saccharin on the position 2 instead of the expected 2-bromo-derivatives :

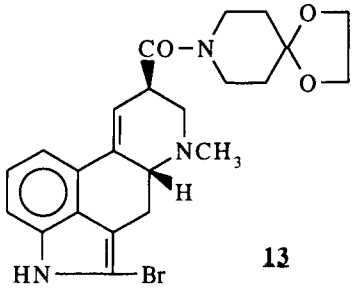


A series of corresponding ergoline and ergolene derivatives was synthesized. The ergotamine derivative showed an interesting antihypertensive activity. Unfortunately, the substance has very poor solubility and stability and therefore the further pharmacological evaluation was stopped (ref. 25).

In the continuation of investigation, new ergolene compounds brominated on the position 2 were prepared :



12a : R_1 = H, R_2 = $CH_2C{\equiv}CH$, X=O,8β
12b : R_1 = H, R_2 = $CH_2C{\equiv}CH$, X=O,8α
12c : R_1 = CH_3, R_2 = $CH_2C{\equiv}CH$, X=O,8β
12d : R_1 = CH_3, R_2 = $CH_2C{\equiv}CH$, X=H_2,8β



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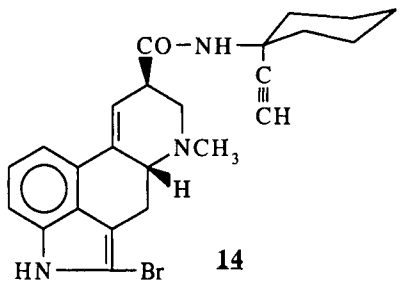

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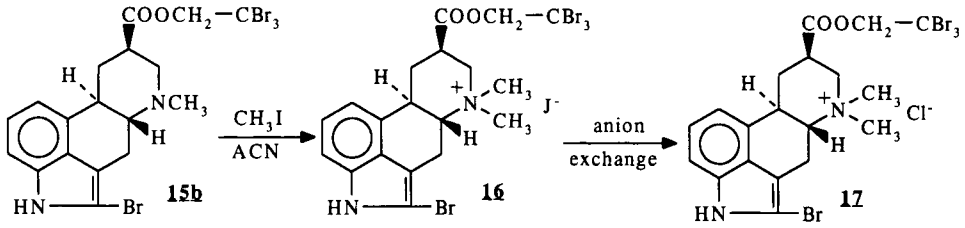
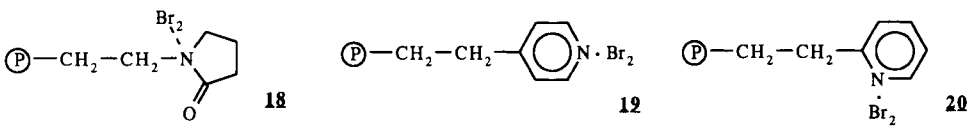


15b 16 17

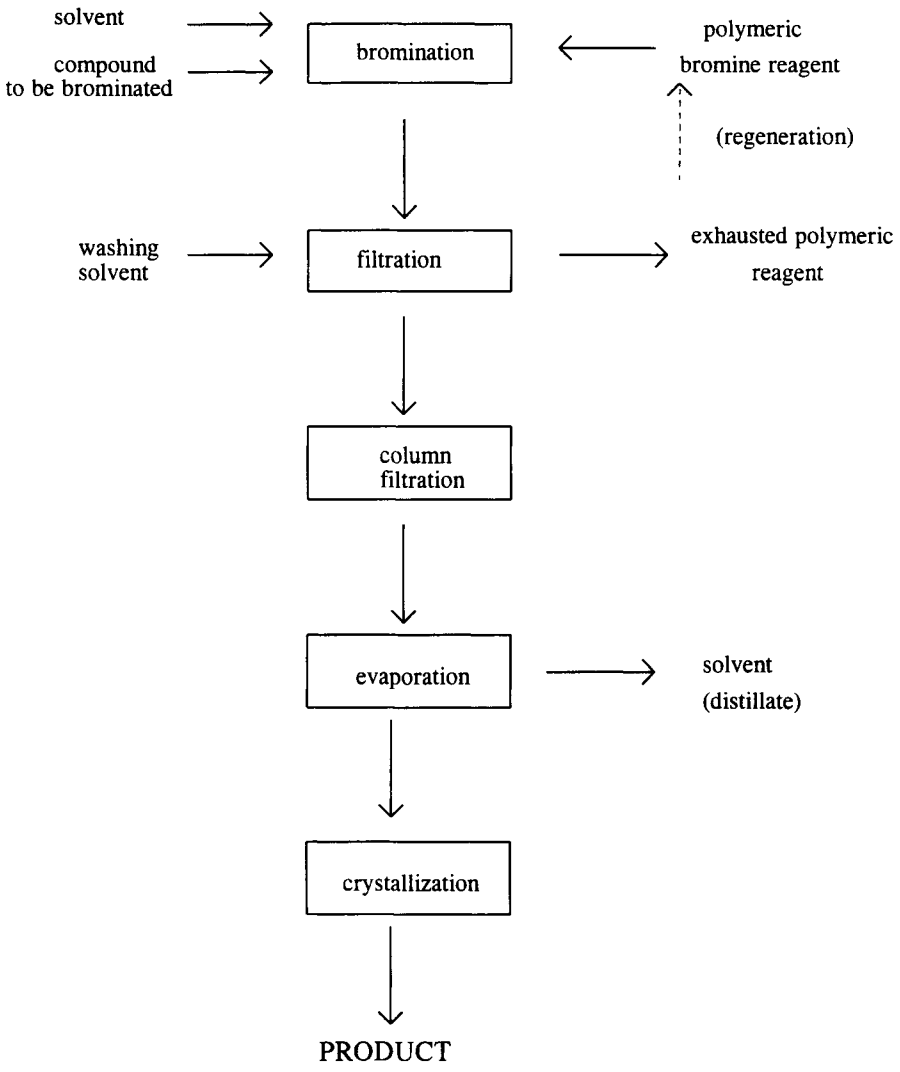
The compounds **13**, **14** and **15** can be prepared from parent lysergic acid amides by bromination with NBS or PHT, but not the compounds of the type **12**. The latter structure is very sensitive and under these circumstances only degradation products were obtained. Besides it was necessary to use much milder reagent, e.g. bromine bonded onto polymeric matrix with polyvinylpyrrolidone or polyvinylpyridine structure (29) :



18 19 20

The advantage of these polymeric reagents is surprisingly simple reaction course, especially in the isolation step. In the majority of cases all extraction procedures are unnecessary. The reaction yields are high and comparable with (good optimized) yields of NBS and PHT processes.

Typical flow sheet of bromination with polymeric bromine reagent :



The selection of appropriate polymeric bromine reagent according to the polymeric structure (step of crosslinking, porosity, step of dilution with styrene, granulation, type of heterocyclic ring incorporated, numbers of N) is very important. From production point of view the use of polymeric reagents reduces the costs for solvents and working hours.

EXPERIMENTAL

As starting compounds commercially available ergot alkaloids (ergotamine, α-ergocryptine etc.) and ergolene or ergoline compounds synthesized during our research work (ref. 30) were used. Melting points were determined with a Kofler microscope and are uncorrected. NMR spectra were recorded on a Varian VXR 300 NMR spectrometer using tetramethylsilane as an internal standard. Microanalyses were carried out by Dept. of Org. Chemistry, Faculty of Natural Science and Technology in Ljubljana. Mass spectra were recorded with mass spectrometer VG - Analytical Auto Spec Q. All optical rotations were determined at sodium D line using a Perkin Elmer polarimeter 141 (1 dm cell). Mass spectra of compounds **5** and **6** were resolved by mr. R. Grahek, LEK; ^{1}H- and ^{13}C-NMR spectra were decoded by dr. D. Kocjan, LEK.

Reaction of ergot alkaloids with N-bromosaccharin

To a suspension of an ergot alkaloid (e.g. : ergotamine), (12.3 mmole) in acetonitrile (200 ml), a solution of N-bromosaccharin (6.43 g, 24.56 mmole) in acetonitrile (110 ml), was added while stirring at room temperature. The solution was allowed to stand in nitrogen atmosphere overnight, the red crystals were filtered off and washed with cold acetonitrile. This substance was purified by chromatography on silicagel column with a mixture of dichloromethane / ethanol (96/4) as an eluent. The dry residue was crystallized from hot ethanol. The compounds with general formula **11** (wherein R is the aminocyclol part of the parent ergot alkaloid) were obtained. The data are listed in table 2.

Table 2. Physico-chemical properties of 2-(2',3'-dihydro-3'-oxo-1',2'-benzisothiazolyl-1',1'-dioxide) derivatives of ergot alkaloids **11**

parent alkaloid	yield of **11**	formula	melting point	$[\alpha]_D^{20}$ C=0.5, $CHCl_3$
ergotamine	45 %	$C_{40}H_{38}N_6O_8S$	190-195°C	- 120°
dihydroergo-tamine	68.2 %	$C_{40}H_{40}N_6O_8S$	191-193°C	- 56.1 °
ergocristine	71 %	$C_{42}H_{42}N_6O_8S$	189-194°C	- 157.8 °
dihydroergo-cristine	96 %	$C_{42}H_{44}N_6O_8S$	184-188°C	- 51.3 °
α-ergocryptine	78.8 %	$C_{39}H_{44}N_6O_8S$	191-196°C	- 157 °
dihydro-α-ergocryptine	81.1 %	$C_{39}H_{46}N_6O_8S$	188-192°C	- 36 °
methyl-9,10-dihydrolysergate	66 %	$C_{24}H_{23}N_3O_3S$	105-110°C	- 48 °

Mass spectra of compounds **11** are characterized by the presence of fission products of the molecule : tricyclic moiety (m/e of fragments depending on alkaloid type) and ergolene moiety with m/e 448 and after SO_2 elimination m/e 384 = 448 - SO_2. The characteristic ^{1}H-NMR is the absence of signal for C - 2 proton and a new multiplet at region 7 - 7.5 ppm for aromatic protons from saccharin moiety.

Isolation and identification of compounds 5 and 6

Mother liquors from the production of bromocriptine **2** were dried by evaporation under vacuum. The dry residue (82.2 g) was applied on chromatographic column (I.D. = 3 cm, lenght = 20 cm) packed with silicagel 60, granulation 0.063 - 0.040 mm and eluted by flash - chromatography with pure dichloromethane. Two separate fractions were obtained and crystallized from dichloromethane (- 15°C).

First fraction contains pure **6** : 2,10'-dibromo-2'(1-bromo-1-methylethyl)-5'α-(2-methyl-propyl)-10',11'-didehydro-12'hydroxi-8α-ergotaman-3',6',18-trione.

Yield : 13.02 g (14.1 %); melting point : 217 - 219°C; $[\alpha]_D^{20} = +220.0°$ (c=1, $CHCl_3$). CHN analysis gave the formula : $C_{32}H_{36}Br_3N_5O_5$. Mass spectrum : M^+ = 808. NMR spectrum ($CDCl_3$, σ - ppm) : 0,9-1,0 (H-18', H-19', 2xd); 1,6-2,2 (H-14', H15', H-16', H-17', m); 2,47 (H-4ax, dd); 2,66 (H-17, s); 2,72 (H-7,dd); 2,96 (H-9', t); 3,0-3,2 (H-5, H-8, m); 3,23 (H-7, d); 3,3o (H-4eq, dd); 3,8-4,1 (H-8', m);4,69 (H-5', dd); 6,44 (H-9, d); 6,8-7,0 (H-12, H-13, H-14, m); 7,28 (H-12', -OH,s);8,71 (H-1, s); 10,50 (H-19, s).

Second fraction contains pure **5** = 2,10'-dibromo-2'-(1-methyethyl)-5'α-(2-methylpropyl)-10',11'-didehydro-12'-hydroxi-8α-ergotaman-3',6',18 trione.

Yield :10.06 g (12.2 %); melting point : 179 -183°C; $[\alpha]_D^{20} = +237.7°$ (C=1, $CHCl_3$). CHN analysis gave the formula : $C_{32}H_{37}Br_2N_5O_5$. Mass spectrum : M^+ = 728. NMR spectrum ($CDCl_3$, σ - ppm) : 0,8 - 1,3 (H-14',H-15', H-18', H-19', 4xd); 1,6-2,2 (H-16', H-17', m); 2,31 (H-13', q); 2,41 (H-4ax, dd); 2,63 (H-17, s); 2,70 (H-7, dd); 2,96 (H-9', t); 3,0-3,2 (H-5, H-8, m); 3,21 (H-7, d); 3,25 (H-4eq, dd); 3,8-4,1 (H-8', m); 4,67 (H-5', dd); 6,40 (H-9, d); 6,7-6,8 (H-12, H13, H-14, m); 7,42 (H-12', OH, s); 9,31 (H-1, s); 10,52 (H-19, s).

Synthesis of 2-bromo-12'-O-ethyl-α-ergocryptine 7

Bromocriptine **2** (0.65 g, 1 mmol) was dissolved in 100 ml of dry ethanol and 60 ml of tetrafluoroboric acid / diethylether complex (85 %) was added while stirring. After standing overnight at RT the solvent was evaporated and the raw product isolated by extraction in the system dichloromethane / 2 % ammonia in water and evaporated to the dry residue. This residue was applied to the chromatographic column (I.D. = 2 cm, lenght = 20 cm) packed with silicagel and eluted with dichloromethane / ethylacetate = 1 : 1. The fractions containing **7** were evaporated to the dry residue and crystallized from alcohol.

Yield : 0.34 g (50 %); MH^+ = 682. Elemental formula : $C_{34}H_{44}BrN_5O_5$. NMR spectrum ($CDCl_3$, σ - ppm) : 0,9-1,3 (H-14, H-15', H-18', H-19', 4xd); 2,68 (H-17, s); 3,6-3,9 (H-8', m); 4,50 (H-5', t); 6,40 (H-9, s); 6,9-7,1 (H-12, H-13, H14, m); 10,35 (H-1, s); 11,72 (H-19,s).

Synthesis of compounds 12

D-lysergic acid propargylamide (0.016 mole) was dissolved in a mixture dichloro-methane/dioxane (85/15), 400 ml. Under vigorous stirring into this solution the polymer supported bromine (prepared acc. to ref. 29) containing 0.024

mole of bromine, was added and stirred for additional 40 minutes. Then the polymeric substance was filtered off and the filtrate evaporated to the dry residue. This residue was subsequently purified on the chromatographic column of silicagel, using a mixture of dichloro-methane / acetone (80/20) as the solvent for elution. The fractions containing the desired compound were dried under vacuum and crystallized.

Table III. Physico-chemical properties of compounds **12**

Compound	Formula	Yield [%]	m.p. [°C]	$[\alpha]_D^{20}$ C=0.5,$CHCl_3$	^{1}H-NMR data (DMSO d_6)
12a	$C_{19}H_{18}BrN_3O$	15.5	169-173	- 78.2	2.47(s, N-CH_3), 3,15(t, ⋮ C-H) 8.50(t, CONH), 11.50(s, NH)
12b	$C_{19}H_{18}BrN_3O$	23.6	183-186	+ 380	2.5(s, N-CH_3), 3,15(t, ⋮ C-H) 8.31(t, CONH), 11.4(s, NH)
12c	$C_{20}H_{20}BrN_3O$	42.9	119-123	+ 30.1	2.49(s, N-CH_3), 3,1(t, ⋮ C-H) 11,15(s, NH)
12d	$C_{20}H_{22}BrN_3$	32.3	208-212	+ 22.8	2.27(s, N'-CH_3), 2,45(s, NCH_3) 3,15(t,⋮ CH), 11.43(s, NH)

Bromination with NBS

Amide of D-lysergic acid with 1,4-dioxa-8-azaspiro-[4,5] decane, prepared acc. to ref. 30, (0.01 mole) was dissolved in a mixture dichloromethane/dioxane (85/15) containing 0.1 g of azobisisobutyronitrile (AIBN). To this solution while stirring at 25-30°C the solution od 0.02 mole NBS in dioxane (50 ml) was added and stirred for 1 hour in nitrogen atmosphere. Then the solution was extracted twice with saturated sodium bicarbonate solution. The separated organic layer was evaporated to dry residue and purified on the chromatographic column (silicagel, dichloromethane-/acetone 90/10 as the eluent). The fractions containing the product **13** where evaporated and the residue crystallized as oxalate salt, $C_{23}H_{26}BrN_3O_3 . C_2H_2O_4$; yield 65.6 %; m.p. : 208-212°C; $[\alpha]_D^{20}$ = +36.2° (C = 0.5, $CHCl_3$).
^{1}H-NMR (DMSO - d6) : 2.47 (s, NCH_3); 3.92 (S, O-CH_2-CH_2-O);
1.56 - 1.75 (m, CH_2-C-CH_2); 3.54 - 3.68 (CH_2NCH_2).
According to the same procedure, the compound **14** : 2-bromo-D-isolysergic acid ethynylcyclohexylamide was obtained. The compound crystallizes from dichloro-methane $C_{24}H_{26}BrN_3O$ x 0.6 CH_2Cl_2; m.p. = 154 - 157°C; $[\alpha]_D^{20}$ = +431.8°

(C = 0.5,MeOH).
^{1}H-NMR (DMSO - d6) : 1.2 - 1.9 (m, 10H cyclohexane); 3.14 (t, : CH)
8.42 (s, CONH); 11.94 (s, NH).

2',2',2'-tribromoethyl 9,10-dihydrolysergate 15a

9,10-dihydrolysergic acid (6.12 g, 0.022 mole), previously dried at 120°C under vacuum, was suspended in pyridine (160 ml) and at 0°C into this solution benzenesulphonyl chloride (11 ml), followed by 2,2,2-tribromoethanol (11.31 g, 0.04 mole) were added. After 2 hours of stirring ice water (160 ml) was added and pH adjusted to 7.0 with saturated sodium bicarbonate (2000 ml). The yellow precipitate was filtered off, dried under vacuum and then recrystallized from hot ethylacetate. Yield of $C_{18}H_{19}Br_2N_2O_2$: 77 % of theory. M.p. : 173 - 175°C.
^{1}H-NMR (DMSO - d6) : 2.35 (s, NCH_3), 4.95 (s, CH_2CBr_3); 11.50 (s, NH).

Bromination of 15a

2',2',2'-tribromoethyl-2-bromo-9,10-dihydrolysergate **15b** was obtained from **15a** according to the procedure described for compound **13**. Yield of **15b**, $C_{18}H_{18}Br_4N_2O_2$, 97 % M.p. = 102 - 104°C, $[\alpha]_D^{20}$ = -41.4° (C=0.5, $CHCl_3$).
^{1}H-NMR (DMSO - d6) : 2.35 (s, NCH_3), 4.95 (s, CH_2CBr_3); 11.32 (s, NH).

Quaternisation of compound 15b

To the solution of **15b** (2.3 g, 3.8 mmol) in acetonitrile (75 ml) methyliodide (7.5 g, 0.05 mol) was added and stirred for 40 min. After standing overnight white crystals were filtered off and dried. Compound **16**, $C_{19}H_{21}Br_4JN_2O_2$ was obtained in yield 87 %. M. p. : 212 - 213°C. ^{1}H-NMR (DMSO - d6) : 3.30 (s, NCH_3, 2x); 5.07 (d, CH_2CBr); 11.64 (s, NH). This compound has very poor solubility in water, therefore was transformed into chloride salt by passing of anion exchange resin charged with Cl^- ion (Lewatit MP 5080). The obtained compound **17** is very soluble in water which enables the pharmacological evaluation. Compound **17** : yield 86 % (from **10**). M.p. : 238 -240°C.
^{1}H-NMR (DMSO - d6) : 3.27 (s, NCH_3 ,2x), 5.10 (d, CH_2CBr_3); 11.92 (s, NH).

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THERMAL REARRANGEMENT OF HEXABROMO-CYCLODODECANE (HBCD)

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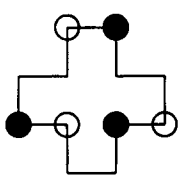
INTRODUCTION

1,2,5,6,9,10-Hexabromocyclododecane (HBCD) is prepared by the bromination of 1Z,5E,9E-cyclododecatriene (CDT). The term "HBCD" will be used here to denote the commercial product containing various isomer compositions. Bromination of CDT leads to three isomers, HBCD-1 (γ), HBCD-2 (β) and HBCD-3(α). All three isomers (Fig. 1) were isolated and fully identified (refs. 1,2).



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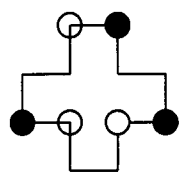

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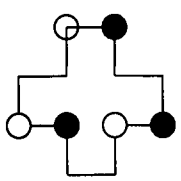

H B C D - 3
1S 2S 5R 6S 9S 10R

Fig. 1. The HBCD-1(γ), HBCD-2(β) and HBCD-3(α) Isomers

HBCD is a white free-flowing product containing about 74 weight percent (w/o) bromine and is recommended as a flame retardant for V-2 EPS, V-2 PP and V-2

HIPS in combination with stabilizers. Four basic types of HBCD are produced by all the HBCD producers, i.e. low melt, medium range, high melt and thermal stabilized HBCD. Analysis of the HBCD manufactured by several producers in given in Table 1 (ref. 3). The melting point of HBCD varies with changes in isomer ratio and composition of impurities.

Table 1. Assay and isomer distribution of commercial samples of HBCD

Sample	% Br	γ-Isomer	α-Isomer	β-Isomer	TBCD*	Unidentified	MP°C
A	--	87.8-89.3	9.5-10.3	<0.5	1.3	ND	198
B	73.8	72.3	13.3	11.7	1.7	1.0	196.5
B-2	73.1	77.0	11.3	9.6	1.5	0.6	207
C	73.1	72.3	12.6	9.5	2.2	3.4	192.2
D	74.5	73.4	12.9	11.4	1.6	0.8	195.5

* TBCD - Tetrabromocyclododecene

Samples A-D were taken from the following materials though not necessarily in the same order :

Bromkal-73-6CD	-	Chemische Fabrik Kalk
FR-1206	-	Dead Sea Bromine Group
CD-75	-	Great Lakes Chemical Corporation
BC-63	-	Saytech
HBCD	-	Societe Potasse et Produits Chimiques

During experiments carried out at the Research and Development Division of the Dead Sea Bromine Group it was found that HBCD indeed decomposes at temperatures above 220°C as reported in the literature (ref. 4) however it was also found that at temperatures below 200°C thermal rearrangement takes place in a reaction not reported heretofore in the literature.

EXPERIMENTAL

Material

Pure isomers were obtained from several crystallizations of HBCD from different sources.

HBCD **1** : Crystallization of commercial HBCD.

HBCD **2** : Bromination of CDT in CCl_4 (ref. 5) and crystallization.

HBCD **3** : Thermal rearrangement of commercial HBCD and crystallization.

Properties of the pure isomers obtained are summarized in Table 2.

Table 2. Pure isomers - Analytical data

Analytical Methods and results	HBCD ISOMERS		
	1 (Γ)	**2** (β)	**3** (α)
mp (°C)	208-210	169-170	171-173
HPLC (w/o)	99.6	99.7	100
RRT* (Zorbax ODS, AN/H_2O 215 nm)	1.0	0.71	0.64
Crystal structure	rhombic	monoclinic	monoclinic
Crystal / Unit cell	8	4	4
TGA** 10°C/min air			
Weight loss w/o at (°C)			
5	249	248	254
10	253	251	258
20	257	253	260

* RRT - Relative retention time for elution in HPLC
** TGA - Thermogravimetric analysis

Analytical Method

Quantitative HPLC analysis was carried out on a Spectraphysics 8720 chromatography system, a rapid scan detector by Barspec on a Zorbax ODS column with acetonitrile water 75/25 as the eluent.

Procedure

A sample of HBCD was weighed in a glass tube dipped in an oil bath with a temperature regulator of ±1°C. During the experiment the sample was monitored for HBr formation. At different times the samples were taken out and cooled to room temperature, weighed and analyzed by quantitative HPLC.

Experiments with pure isomers and isomer mixtures were conducted at temperatures varying from 160-200°C. The experiments were conducted for several hours and at temperatures lower than 180°C. The results of the experiments with pure isomers at 190°C are given in Tables 3,4 and 5. HPLC analysis is normalized. The actual total represents the total amount (by HPLC analysis) of the three isomers. It is used as an indicator for the side reaction(s).

Table 3. Experimental results for thermal rearrangement of HBCD-1 at 190°C

Time	Weight Loss	ISOMERS (%)			
		Normalized %			Actual
(min)	(%)	1	2	3	Total
0	0	99.6	0.2	0.2	100.0
10	0.2	93.3	0.8	5.9	100.1
20	0	79.7	2.6	17.7	100.5
30	(0.1)	13.9	11.7	74.7	102.6
45	0.3	8.4	11.7	79.9	101.2
60	0	10.9	11.7	77.7	101.6
120	4.2	14.8	11.3	73.9	101.1
Average of actual total					101.2±0.8

Table 4. Experimental results for thermal rearrangement of HBCD-2 at 190°C

Time	Weight Loss	ISOMERS (%)			
		Normalized %			Actual
(min)	(%)	1	2	3	Total
0	0	0.1	99.7	0.2	100.0
10	0	6.9	53.0	40.1	101.2
20	(1.0)	7.4	26.9	65.7	103.6
30	0.5	7.3	21.7	71.0	103.2
45	1.0	7.6	15.5	76.9	104.2
60	0.2	8.5	14.4	77.1	101.6
120	4.2	15.1	12.7	72.2	101.5
Average of actual total					102.9±1.2

Table 5. Experimental results for thermal rearrangement of HBCD-3 at 190°C

Time	Weight Loss	ISOMERS (%)			
		Normalized %			Actual
(min)	(%)	1	2	3	Total
0	0	0	0	100	100
10	(0.8)	4.3	4.6	91.1	100.5
20	(0.6)	6.7	8.3	85.0	100.6
30	(0.4)	6.9	10.8	82.3	101.2
45	2.5	7.6	12.4	80.0	105.2
60	0.4	7.6	12.4	80.0	105.2
120	0.8	10	12.3	77.7	105.2
Average of actual total					103.0±2.3

Discussion

Isothermal decomposition

Decomposition time was defined as the time taken for weight loss greater than 5 weight %. Results are presented in Table 6. No substantial differences between the three isomers can be discerned from the results. At temperatures up to 190°C isomers **2** and **3** are more resistance to thermal decomposition than isomer **1**. Larsen (ref. 3) reported decomposition time to be 40-110 min. at 195°C for commercial HBCD (Table 1).

Table 6. Time (Minutes) for decomposition greater than 5 weight %

Temp	ISOMERS		
(°C)	1	2	3
170	300	300+	300+
180	180	180+	180+
190	60+	60+	120
200	30	30	20+

Thermal rearrangement of trans-1,2-dibromo compounds is known in the literature (refs. 6-10). In all case studies only one pair of bromine in each organic molecular was studied. Bellucci (ref. 10), for example, studied the kinetics of such trans-1,2-cyclo alkanes as cyclopentane, hexane, octane, etc. The intermediates suggested as an explanation for the experimental results are bromonium bromide I in polar solvents and four center transition state II in non-polar solvents.

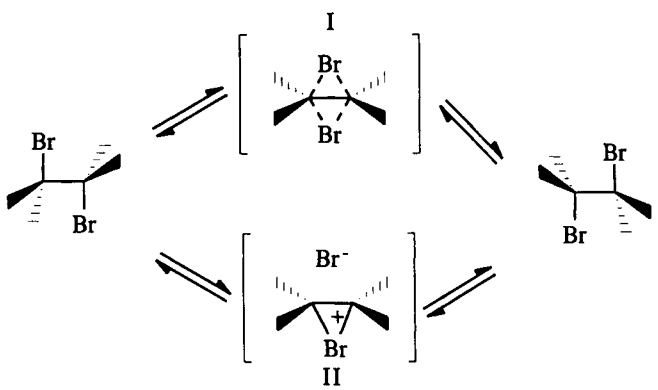

Fig. 2. Transition state

Experiments were undertaken in various organic solvents and over a wide range of temperatures.

Thermal rearrangement

Only two types of behavior were noted when the samples of pure isomeric HBCD or the mixtures were heated - thermal decomposition or thermal rearrangement. By way of example, we will discuss the results presented in Table 3. Isomer **1** with a purity of 99.6 % was heated to 190°C. Samples were taken every first 10 min for two hours and were weighed after cooling. Weight loss until the end of the first hour was negligible within experimental error. The samples were ground and analyzed for each of the three isomers. The total of all three isomers was within the range of 100+3% which we believe to be the cumulative analytical error. The results were normalized and presented as the isomer normalized %. HBCD **1** and HBCD **3** have two-fold rotation axis C_2 symmetry whereas HBCD **2** does not. The fact that isomer **2** is predominant during thermal rearrangement indicates that more than one pair of trans,1,2-dibromine is involved. It is reasonable to believe that at experimental temperature rearrangement is a dynamic process.

The following observations can be made from Table 3-5 :

1. Each isomer rearranges to give a final mixture of the same isomeric composition.
2. During thermal rearrangement no side reaction takes place.
3. The isomer ratio of each sample lies within analytical error (about 3%).
4. Rearrangement of each isomer or isomeric mixture leads to only one of the three isomers. No side reaction such as "bromine dancing", trans-annulare reaction etc, can be observed.

Calculated thermal isomerization of isomer **2** at 170°C based on experimental results confirms the pattern (Fig. 3).

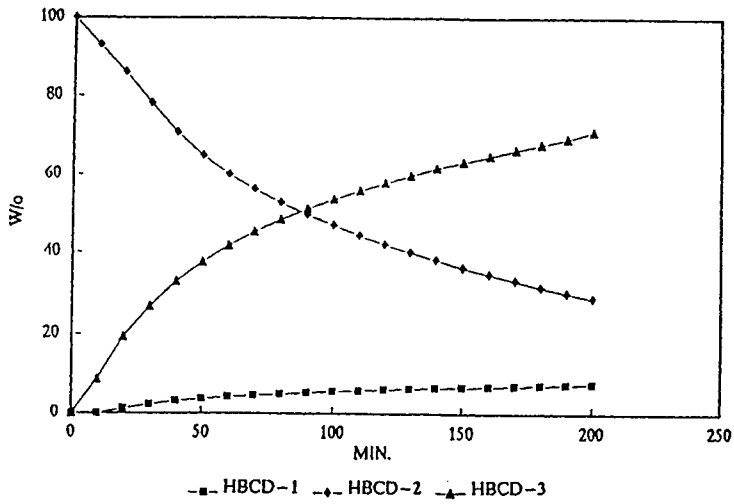

Fig. 3. Calculated thermal isomerization - HBCD **2** at 170°C

Isomer ratios were calculated based on twenty experiments performed on pure isomers and mixtures at temperatures between 160-200°C. The results presented in Figure 4 indicate that regardless of the starting isomer there seems to be an isomeric ratio that serves as a "thermal sink". The predominant isomer at the equilibrium is isomer **3** although the predominant isomer in commercial HBCD is isomer **1**. Customer preference for a higher content of isomer **1**, i.e. highmelting HBCD, cannot be accounted for by its higher thermal stability. Based on these experiments it can be concluded that the preference for higher melting HBCD is due to that fact that special care is taken to reduce the level of impurities during the preparation of this type of HBCD. This conclusion is also drawn by Valange et al (ref. 2) "... thermal stability of commercial HBCD is very dependent upon the purification process..."

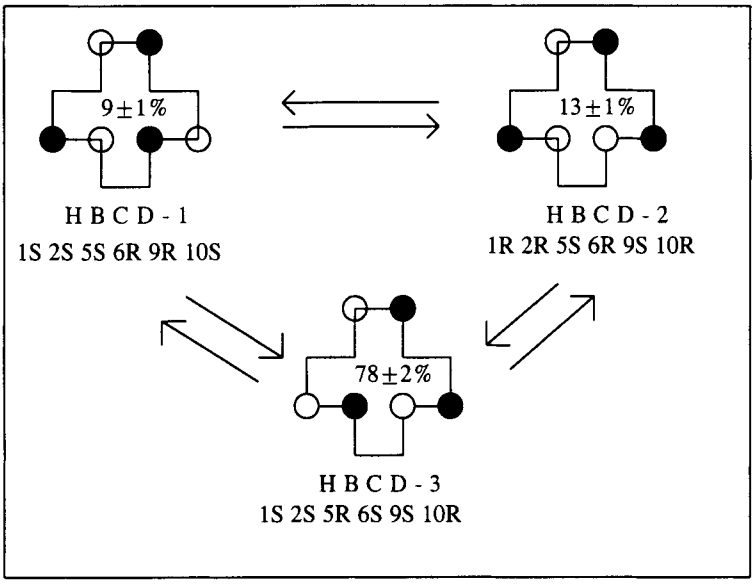

Fig. 4. Isomer ratio at thermal equilibrium ("thermal sink")

Conclusion

The thermal rearrangement of HBCD and pure isomers was studied. We found that all isomers thermally rearrange to give the same final isomer distribution. During this rearrangement no evidence was found for "bromine dancing" on the ring. No side reaction was detected. The longer the time and the higher the temperature the greater thermal degradation of the HBCD occurred. Thermal equilibrium consists of 78 % isomer **3**, 13% isomer **2** and 9 % isomer **1**.

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STEREO-, REGIO- AND CHEMOSELECTIVITY OF BROMINATION OF ETHYLENIC COMPOUNDS

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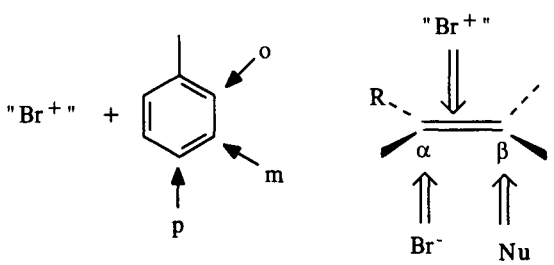
Systematic studies of the selectivity of electrophilic bromine addition to ethylenic bonds are almost inexistent whereas the selectivity of electrophilic bromination of aromatic compounds has been extensively investigated (ref. 1). This surprising difference arises probably from particular features of their reaction mechanisms. Aromatic substitution exhibits only regioselectivity, which is determined by the bromine attack itself, i.e. the selectivity- and rate-determining steps are identical,



Scheme 1. Selectivity of electrophilic bromine addition.

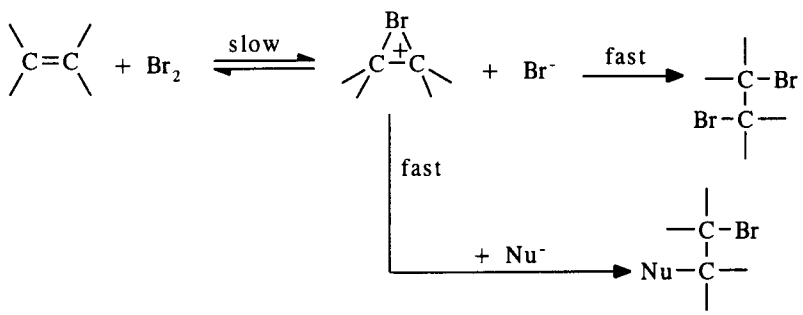
Whereas the three possible selectivities, stereo-, regio- and chemo-selectivity, of bromine addition are determined in steps posterior to the formation of the ionic intermediate. Bromine addition is, therefore, more complex than bromine substitution, as regards the variety of the selectivities and as regards the mechanistic aspects which determine the product formation.

The absence of established rules for understanding the selectivity of the bromination of carbon-carbon double bonds explains probably why this

straightforward reaction is not frequently used in synthetic organic chemistry. Nevertheless, bromination, as it is presented in textbooks, could lead to a variety of interesting products, such as bromoesters, bromoethers, bromoamides, bromofluorides, etc..., containing an easily transformable carbon-bromine bond in the α-position with respect to the functional group derived from the added nucleophile.

Many mechanistic results on this electrophilic addition are available but most of them deal with the first steps of the reaction in which the ionic intermediate is formed, rather than with the last steps in which the products are obtained by nucleophilic attack on this intermediate (ref. 2). The present paper reports results on the selectivity of olefin bromination, which have been obtained more or less systematically with a view to improving the existing rules which are too naive to be useful in synthesis (ref. 3).

The simplified mechanism shown in Scheme 2 focuses attention on the ionic intermediate which is presented in the usual form of a bromonium ion although it is now well known that it can be an open β-bromocarbocation (ref. 4).

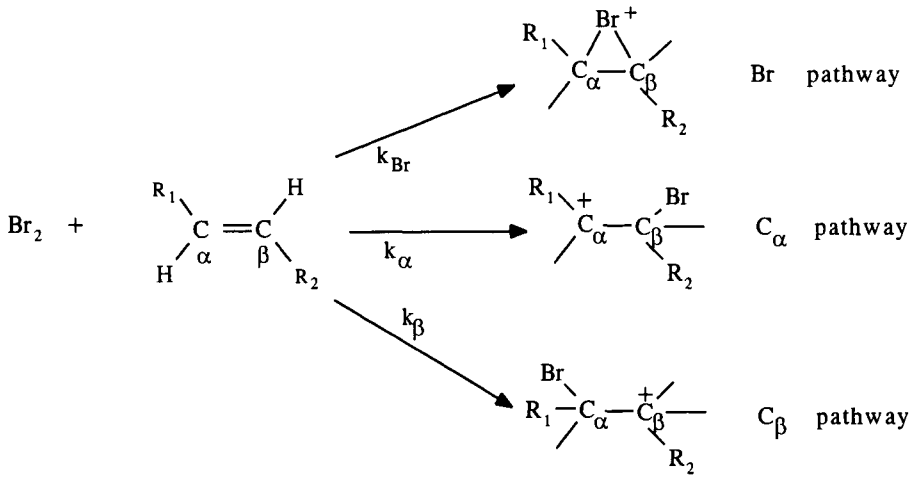


Scheme 2. Simplified mechanism of bromine addition.

The product selectivity arises from the reaction of this intermediate with the various nucleophiles present in the reaction medium. Therefore, the structure of this intermediate and its close environment (counter-ion, solvent molecules, etc.) determines the product selectivity. It is important to note that the relevant data concern the intermediate as it is formed during the reaction and not prepared under extreme conditions where it is stable, such as those used to obtain the nmr spectra of these ions, for example (ref. 5). Since the life-time of this ionic species in the reaction medium is very short, in the 10^{-9} - 10^{-10} s range (ref. 6), there is no way to observe it directly. Consequently, the available data, useful for understanding

product selectivity, can only be obtained from the first ionization steps, i.e. from kinetic data measured under particular conditions.

Some years ago, we tackled (ref. 7) the particular question of bromine bridging, related mainly to stereochemistry, postulating that bromonium ions and bromocarbocations are formed in separate pathways as shown in Scheme 3. The relative rates of reaction by these pathways depend on the olefin structure. As demonstrated later



Scheme 3. Bromonium ions and bromocarbocations

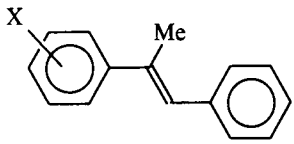
by calculations (ref. 8), this working hypothesis implies that there is no equilibrium between the three cations. From the comparison of the effects of the two substituents either on C_α or on C_β, we were able to measure the symmetry of the charge development in the intermediates. If the kinetic effect of modifying R_1 is the same as for R_2, the charge distribution is symmetrical and the intermediate is a bromonium ion. If the effect of R_1 is significantly greater than that of R_2, the intermediate is the C_α carbocation; if it is smaller, the C_β cation is the intermediate. This principle was applied to a large variety of olefins (ref. 4). The results showed three distinct classes of olefin, the bromination of which goes either through open β -bromocations only, or through fully bridged bromonium ions or through partially bridged ions when the carbocationic and bromonium pathways compete.

The first class was found when the olefin substituents are highly conjugated with the double bond, the second class when there is no resonance between the substituents and the π-bond and the last class when the substituents are moderately conjugated with the double bond.

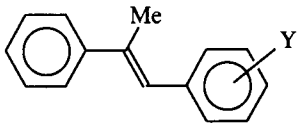
COMPLETELY REGIO- AND CHEMOSELECTIVE BROMINATION OF HIGHLY CONJUGATED ALKENES

When a substituent is able to resonantly stabilize the positive charge of the ionic intermediate, there is no bromine bridging and the intermediate is an open β-bromocarbocation. These carbocations have been shown to occur in the bromination of α-methylstilbenes (ref. 9), **1** and **2**, and of a variety of enol ethers (ref. 10) and acetates (ref. 11).

When the multipathway scheme (Scheme 3) was applied to the first series, we obtained (ref. 9) a highly negative ρ-value (-4.6) for the kinetic effect of the substituent X in **1** and a significantly smaller value (ρ = -1.7) for the effect of Y in **2**, at least as long as Y is less electron-donating than a p-methyl group. From the ρ-ratio, we were able to demonstrate

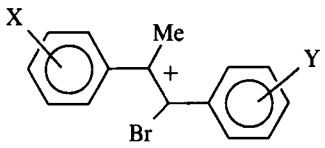


1



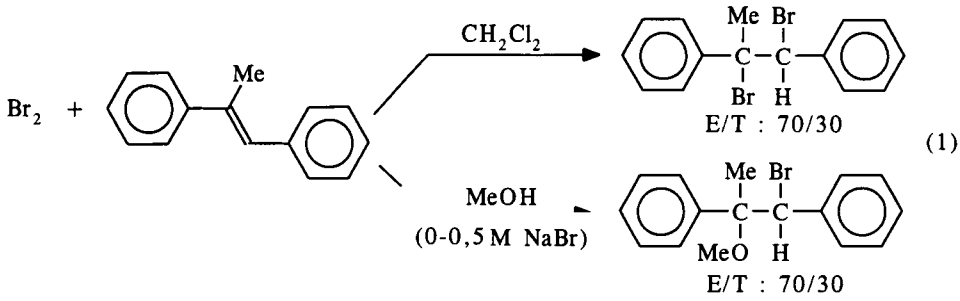
2

that the tertiary benzylic carbocation **3** is the sole bromination intermediate. In agreement with the absence of bromine bridging, the bromination of olefins **1** and **2** is not 100 % stereoselective.



3

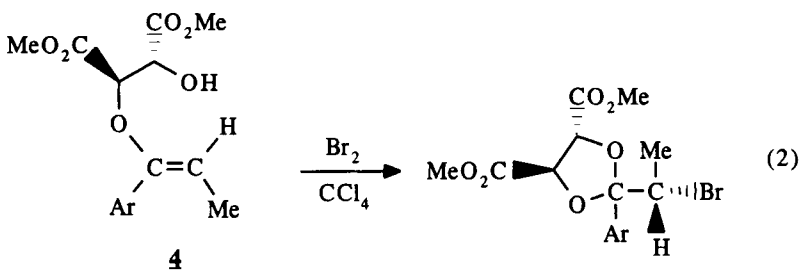
The bromination products, dibromide in methylene chloride and methoxybromide in methanol, are a mixture of erythro- and threo-diastereoisomers, obtained in a ratio, Erythro/Threo = 70 / 30, which does not depend on the substituents or on the solvent. As expected, the reaction in the protic solvent is fully regioselective, i.e. methanol only traps the intermediate



(1)

on its tertiary carbon atom (eqn. 1).The chemo-selectivity, i.e. the competition between the solvent and the bromide ion in their nucleophilic reactions with intermediate **3**, is more unexpected. Only solvent-incorporated adducts are obtained, even when sodium bromide is added to the reaction medium in concentration as high as 0.5 M. The bromination of these highly conjugated alkenes is totally chemoselective in favour of the protic solvent, a stronger nucleophile than the potentially competing bromide ion.

Analogous results were obtained for enol ether bromination. The reaction of ring-substituted α-methoxy-styrenes (ref. 12) and ethoxyvinylethers (ref. 10), for example, leads to solvent-incorporated products in which only methanol attacks the carbon atom bearing the ether substituent. A nice application of these high regio- and chemoselectivities is found in the synthesis of optically active 2-alkylalkanoic acids (ref. 13). The key step of this asymmetric synthesis is the regioselective and chemoselective bromination of the enol ether **4** in which the chiral inductor is tartaric acid, one of the alcohol functions of which acts as an internal nucleophile (eqn. 2).



(2)

4

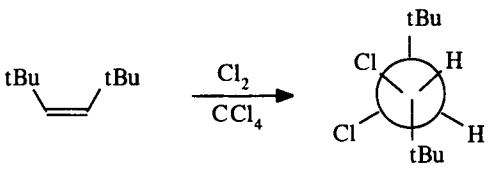
STEREOSELECTIVE AND ANTI-MARKOVNIKOV BEHAVIOUR OF NON-CONJUGATED ALKENES

When there is no conjugated substituent able to stabilize the positive charge development, the bromine atom is involved in the charge stabilization and the

bromination intermediate is a fully bridged bromonium ion. It has been shown from kinetic data that the charge distribution in bromination transition states, and therefore, in the ionic intermediates of the electrophilic reaction of alkenes bearing one or several alkyl or allyl substituents in various relative positions is symmetrical (ref. 14). This result was taken as evidence that only bromonium ions occur along the bromination pathway of these non-conjugated alkenes, in methanol or acetic acid. In the light of the following stereochemical results, this conclusion seems to be valid, whatever the solvent.

At present, this rule fails only when functional neighboring substituents, capable of anchimeric assistance and in a convenient position with respect to the developing positive charge, can compete with bromine in the charge stabilization of the cationic intermediate (ref. 15). For example, the reaction of some unsaturated alcohols (ref. 16) goes through five- or six-membered cyclic oxonium ions, rather than through bromonium ions.

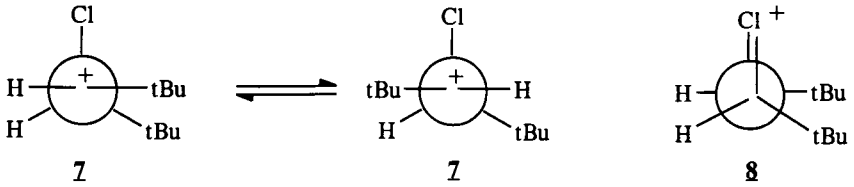
According to the early postulate of Roberts and Kimball (ref. 17), the reaction of non-conjugated olefins is always 100 % stereoselective (anti-addition, exclusively) and stereospecific (cis and trans isomers lead to different diastereoisomers) and always involves bromonium ions. An elegant demonstration of the generality of this ancient claim was given by Fahey (ref. 18). The chlorination of the highly strained cis-di-*tert*-butylethylene, **5**, leads to the corresponding dl-dichloride **6**, only, although the β-chlorocarbocation, **7**, in which steric repulsions between the two tert-butyl groups can be minimized, should be favoured as compared with the strained chloronium ion, **8** (eqn. 3).



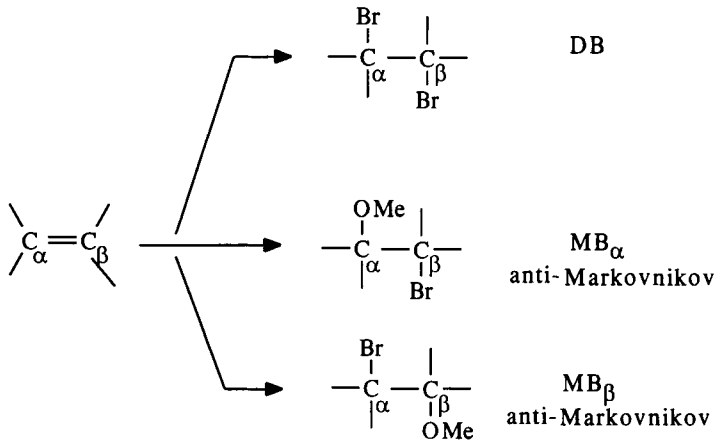
100 % dl (3)

5 **6**

If, even in this extremely unfavourable case involving chlorine, a poorer bridging atom than bromine, bridging is enforced, bromine bridging must occur a fortiori for generally less crowded alkenes.



Apart from information on stereochemistry, bromine bridging does not provide a priori any rule regarding regio- and chemoselectivity. Therefore, we systematically investigated (ref. 3) these two selectivities in the bromination of ethylenic compounds substituted by a variety of more or less branched alkyl groups (Scheme 4).



Scheme 4. Selectivities in the bromination of ethylenic compounds

Methanol containing 0.2 M sodium bromide was chosen as the reaction medium. Bromide ions were added to obtain better precision on chemoselectivity since, in the absence of external bromide, the yield of dibromo adduct can be very small. The results of this investigation are shown in Table 1.

Table 1. Regio-[a] and Chemoselectivity[b] of Alkene Bromination[c] in Methanol, 0.2 M NaBr, at 25°C

R	% Mark [a]	% DB [b]
RCH=CH$_2$		
Me	82	39
Et	72	47
iPr	19	60
tBu	0	70
RMeCH=CH$_2$		
Me	100	15
Et	100	20
iPr	100	26
tBu	100	21
neoPe	100	12
cis-RCH=CHMe		
Me	-	41
Et	37	48
iPr	22	51
tBu	0	65
trans-RCH=CHMe		
Me	-	37
Et	29	41
iPr	0	45
tBu	0	43

a) Regioselectivity : % Mark = % Markovnikov addition = 100 x $MB_\alpha/(MB_\alpha + MB_\beta)$ with MB = methoxybromoadduct; b) Chemoselectivity : % DB = % dibromide = 100 x [DB / (DB + MB_α + MB_β)]; c) Data taken from Ref. 3.

As regards the regioselectivity of monosubstituted, cis and trans disubstituted alkenes, bromination most frequently exhibits anti-Markovnikov behaviour. Only in the case of propene and 1-butene, i.e. when the double bond bears only one linear substituent, bromination in methanol is predominantly but not completely Markovnikov. Steric effects obviously play an important role in determining the

major anti-Markovnikov behaviour of alkenes bearing a branched substituent such as *iso*-propyl or *tert*-butyl. Moreover, the anti-Markovnikov adducts are more important for trans alkenes than for their less congested cis isomers. However, steric effects are not the only regiochemistry-determining factors, since anti-Markovnikov adducts are predominant even for the non-bulky Et, Me alkenes, **19** and **23**. Moreover, gem-alkenes, the geminatet carbon atom of which is not readily accessible to nucleophile for steric reasons, react exclusively according to the Markovnikov rule, whatever the crowding of the substituents.

The Markovnikov regioselectivity of the gem-alkenes is associated with a chemoselectivity, in favour of methanol attack, significantly greater than that observed for the other alkenes. If no sodium bromide is added to the reaction medium, no dibromide is observed for this series. Therefore, these alkenes behave as highly conjugated olefins, as regards their regio- and chemo-selectivity. In other words, the bromination intermediates of gem-alkenes resemble β-bromocarbocations, rather than bromonium ions. Theoretical calculations (ref. 8) but not kinetic data (ref. 14) support this conclusion.

This conclusion can probably be extrapolated to trisubstituted alkenes[14] since trimethylethylene affords 19 % dibromide and the Markovnikov methoxy-bromoadduct only (ref. 3).

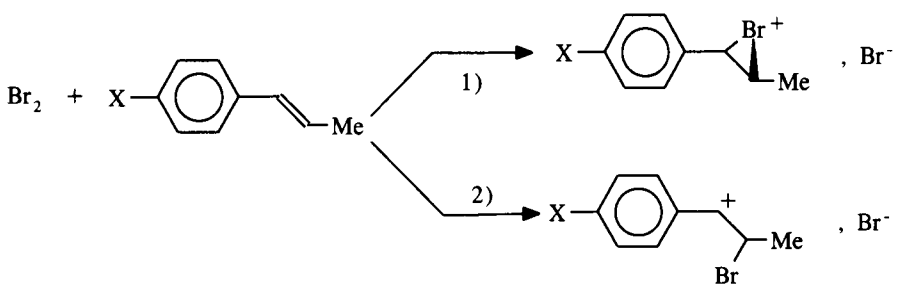
The chemoselectivity of the other alkenes of Table 1 is more variable. It appears that bulky substituents favour bromide over methanol attack of the bromonium ion, since dibromide increases from 39 to 70 % on going from methyl to *tert*-butyl in the monosubstituted series. The same trend is observed in the disubstituted series with a contraction of the chemoselectivity span (37 to 43 % on going from methyl to *tert*-butyl) for the trans isomers. Since the solvated bromide ion can be viewed as a nucleophile larger than methanol, the influence of steric effects, important in determining the regioselectivity, does not seem very significant as regards the chemoselectivity. This result has been interpreted in terms of a different balance between polar and steric effects of the substituents on these two selectivities.

However, mechanistic features not involved in the simplified mechanism of Scheme 2 can also play a role. In particular, interaction of the bromonium-bromide ion pair with its close solvent environment, which cannot be readily estimated from kinetics or product formation in bromination. An example of this control is shown in the following paragraph.

STEREOSPECIFIC AND 100 % REGIOSELECTIVE BROMINATION OF A MODERATELY CONJUGATED OLEFIN

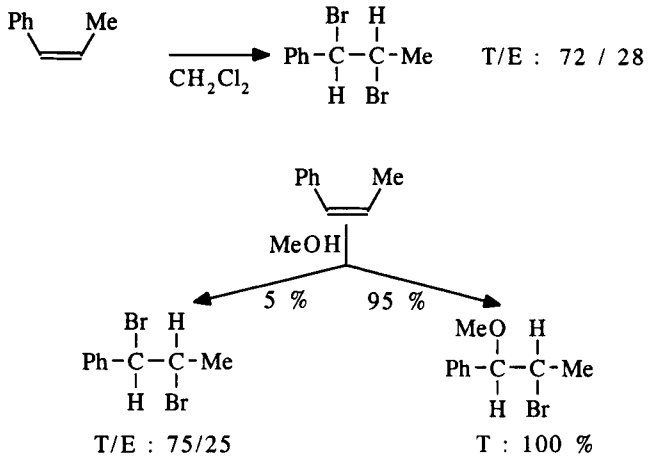
In the bromination of β-methylstyrenes, kinetic data (ref. 19) show that, depending on the substituents, there is competition between carbocationic and bromonium pathways (Scheme 5). For strongly electron-donating substituents (4-OMe, for example), only path 2, is followed whereas for strongly withdrawing groups (3,5-$(CF_3)_2$, for example) path 1 is the sole reaction pathway. For the unsubstituted parent (X=H), path 2 represents about 90 % of the reaction. This competition does not vary with the solvent significantly, similar results being obtained in methanol, acetic acid or methylene chloride.

When the bromination of the unsubstituted β-methyl-styrenes (ref. 19) is carried out in methylene chloride, the two diastereoisomeric dibromides are obtained in ratios of 72 threo/28 erythro and 20 threo/80 erythro for the cis and trans isomers, respectively. This result agrees fairly well with a partially bridged intermediate, since the corresponding benzylic carbocation leads to a 65 erythro/35 threo ratio (ref. 20). When the same reactions are carried out in methanol, the



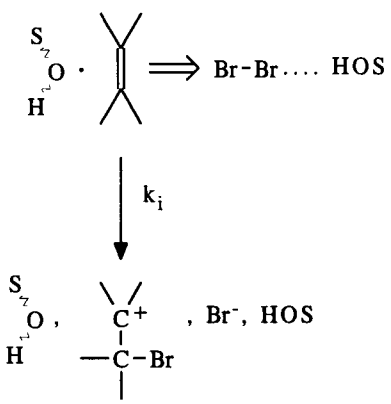
Scheme 5. Competition between carbocationic and bromonium pathways.

predominant bromination products are the bromomethoxyadducts which are obtained 100 % regioselectivity, 100 % stereoselectivity and stereospecifically, the cis olefin leading only to the threo isomer whereas the trans affords only the erythro isomer. This result is all the more surprising that the small amount of dibromide (5 %) exhibits the same stereochemistry as that observed in the non protic methylene chloride (Scheme 6). This can be understood when the following results of an extensive study of kinetic solvent effects are considered.



Scheme 6. Bromination of β-methyl-styrenes in CH_2Cl_2 or in MeOH.

It has been shown (ref. 21) that a solvent which is both protic and nucleophilic, assists the formation of the bromination intermediates of moderately reactive olefins as styrenes in two ways, (Scheme 7). Firstly, the solvent initiates bromide ion formation electrophilically and, secondly, favours



Scheme 7. Role of solvent in the formation of intermediates

positive charge development nucleophilically. In agreement with this nucleophilic assistance, a solvent molecule is included in the bromination intermediate, as soon as it is formed, in a position suitable to trap it, prior to any other nucleophile reaching it or to any rearrangement occurring (ref. 22). As a consequence, the major bromination product is the solvent-incorporated adduct with a stereochemistry anti with respect to the first bromine atom.

This stereospecific reaction is, therefore, a rare example of stereochemical control by nucleophilic solvent assistance of an ionization process.

CONCLUDING REMARKS

Apart from the particular example of the moderately conjugated styrenes, the reaction of which involves partially bridged bromonium ions and nucleophilic solvent assistance, the stereochemistry of olefin bromination is directly related to bromine bridging in the intermediates. Non-conjugated alkenes react via bromonium ions and their reaction is 100 % stereoselective and stereospecific. In contrast, the reaction of highly conjugated olefins goes through open β-bromocarbocations and exhibits a stereoselectivity similar to that observed in carbocation chemistry.

The regiochemistry of these conjugated alkenes is in agreement with the carbocationic character of their intermediates. As regards the non-conjugated alkenes reacting via bridged ions, the Markovnikov rule does not apply systematically, the anti-Markovnikov adduct being predominant in many examples which do not necessarily involve large steric effects. Consequently, the Markovnikov rule and the associated role of the polar substituent effects have to be reexamined for this electrophilic addition. The only case of a complete Markovnikov bromination is found for the gem-alkenes, the intermediates of which closely resemble carbocations.

The chemoselectivity of bromination going through bromocarbocations (highly conjugated olefins and also gem-alkenes) is 100 % in favour of methanol, a nucleophile stronger than bromide ions. However, when the intermediates are bromonium ions, the chemoselectivity is poor. Branched substituents seem to favour the dibromide over the solvent-incorporated adduct, although the bromide ion is considered to be a bulkier nucleophile than methanol.

Most of these results have been obtained in methanol but some of them can be extrapolated to other solvents, if the following solvent effects are considered. Bromine bridging has been shown to be hardly solvent-dependent.[2] Therefore, the selectivities related to this feature of bromination intermediates do not significantly depend on the solvent. When the intermediates are carbocations, the stereoselectivity can vary (ref. 23) widely with the solvent (ref. 24), insofar as the conformational equilibrium of these cations is solvent-dependent. Nevertheless, this equilibration can be locked in a nucleophilic solvent when it nucleophilically assists the formation of the intermediate. Therefore, as exemplified in methylstyrene bromination, a carbocation can react 100 % stereoselectivity.

In the absence of more elaborate methods of observing of short-lived bromination intermediates, the present results can provide some useful empirical rules, the most important being as follows.

i) The bromination of cis and trans non conjugated olefins is stereospecific, whatever the crowding of the double bond, the solvent and the nucleophiles. The regioselectivity is not complete and frequently in disagreement with the Markovnikov rule, not only for steric reasons.

ii) The reaction of highly conjugated olefins, of gem-alkenes and probably of trisubstituted alkenes is 100 % regioselective and 100 % chemoselective in favour of the strongest nucleophile.

iii) The behaviour of monosubstituted non-conjugated olefins is more versatile as regards their regioselectivity and chemoselectivity, and is more difficult to predict a priori. These uncertainties can probably be eliminated by a better understanding of the structure and the reactivity of bromonium ions.

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THE FATES OF BROMONIUM IONS IN SOLUTION : A VERY SHORT LIFETIME WITH MANY DIFFERENT ENDINGS

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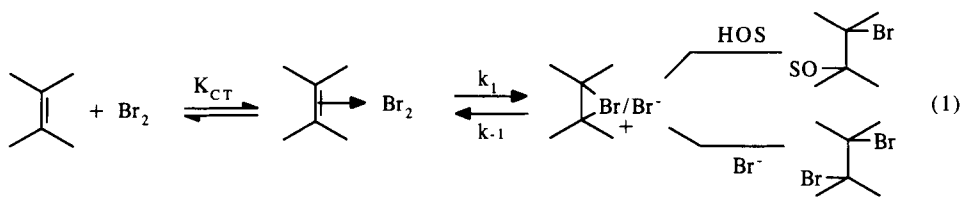
INTRODUCTION

The generally accepted mechanism for electrophilic bromination of olefins in hydroxylic solutions of medium to high polarity, and at low [Br_2], is given in equation 1 (ref. 1).



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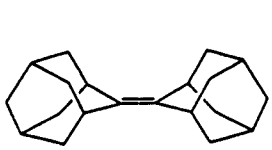
What concerns us here are three topics addressing the fates of bromonium ions in solution and details of the mechanism for the addition reaction. In what follows, we will discuss the x-ray structure of the world's only known stable bromonium ion, that of adamantylideneadamantane, (Ad-Ad, **1**) and show that it is capable of an extremely rapid degenerate transfer of Br^+ in solution to an acceptor olefin. Second, we will discuss the use of secondary α-deuterium kinetic isotope effects (DKie) in mechanistic studies of the addition of Br_2 to various deuterated cyclohexenes **2,3**. Finally, we will explore the possibility of whether a bromonium ion, generated in solution from the solvolysis of *trans*-2-bromo-1-[(trifluoromethanesulfonyl)oxy]cyclohexane **4**, can be captured by Br^- on the Br^+ of the bromonium ion, thereby generating olefin and Br_2. This process would be

relevant to the question of whether bromonium ions can be formed reversibly during electrophilic Br_2 addition to olefins.



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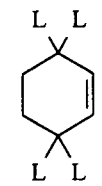

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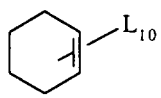
b L = D



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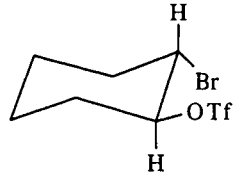

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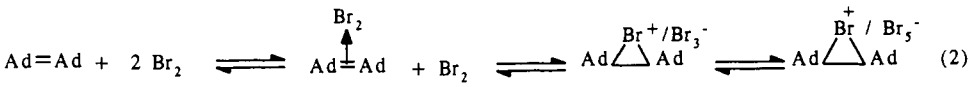
The Bromonium Ion of Adamantylideneadamantane

When Ad=Ad **1** is treated with Br_2 in chlorinated hydrocarbons, an immediate precipitation of a yellow solid material is observed (ref. 1) That material proves to be the bromonium ion/Br_3^- salt (refs. 1,2) which, when redissolved in such solvents as $ClCH_2CH_2Cl$ or $CH_3C{\equiv}N$, instantly establishes the equilibrium shown in equation 2 (ref. 3). The presence of all these rapidly interconverting species precludes simple



(2)

study of any one entity in solution. However, this problem can be circumvented by trapping of the nucleophilic Br_3^- simply by treatment of the mixture with methyltriflate (CH_3OTf) (ref. 4). This reaction converts Br_3^- into CH_3Br and Br_2 : after evaporation of all volatiles, a white solid is obtained that can be crystallized from CH_2Cl_2/hexane (ref. 4). X-ray diffraction studies of the crystalline material shows it to be the bromonium ion triflate, the structure of which is shown in Figure 1 (ref. 5). The bond lengths and angles of interest are C_{10}-C_{20} (C_{30}-C_{40}), 1.492 Å (1.491 Å);Br-C_{10} (Br-C_{30}), 2.118 Å (2.089 Å); Br-C_{20} (Br-C_{40}), 2.136 Å (2.114 Å); and C_{10}-Br-C_{20} (C_{30}-Br-C_{40}), 41.0° (41.6°); Br-C_{20}-C_{10} (Br-C_{40}-C_{30}), 68.8° (68.3°);

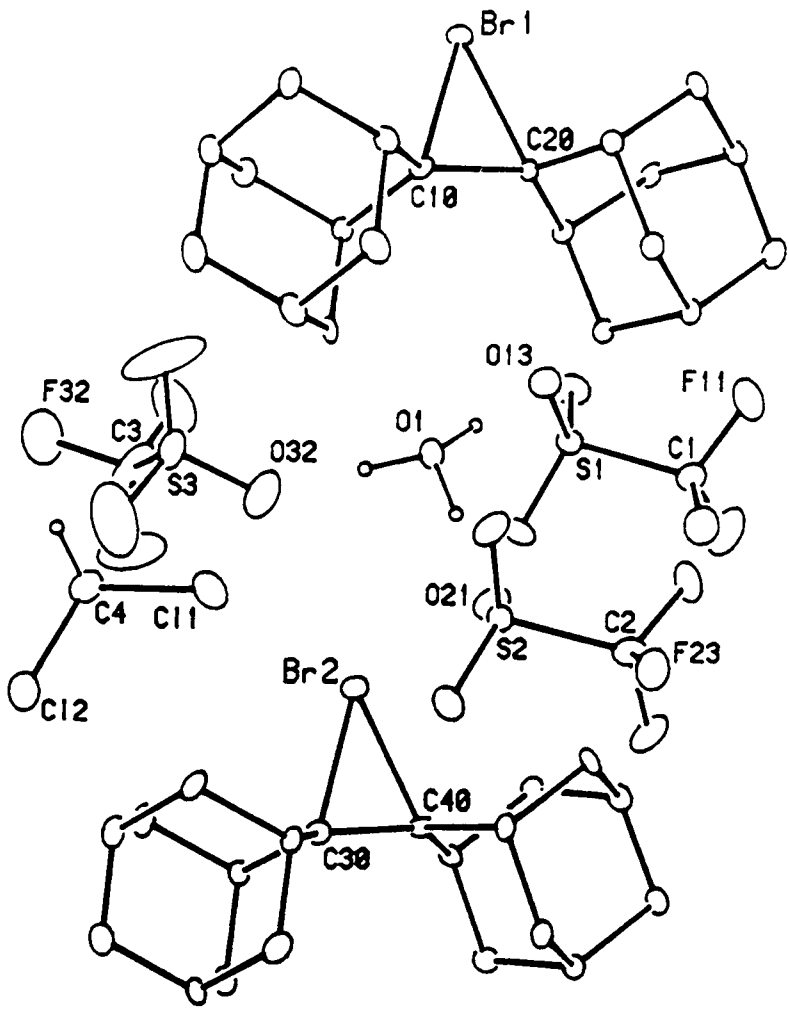
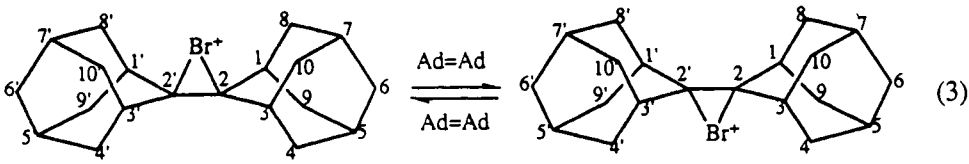


Figure 1. A view of the asymmetric unit of the bromonium triflate of Ad=Ad showing two independent bromonium ions in the unit cell with a separating layer consisting of 1 H_3O^+, 1 CH_2Cl_2, and 3 $CF_3SO_3^-$ moieties. Atoms are represented as Gaussian ellipsoids at the 20 % probability level.

Br-C_{10}-C_{20} (Br-C_{30}-C_{40}), 70.1° (70.2°). The structure of the bromonium triflate[5] compares favorably with that reported earlier for the Ad=Ad bromonium ion tribromide (ref. 2) with the important exception that the Br-C bondlengths in the latter differed by ~ 0.07 Å (2.116 vs 2.194 Å), the asymmetry being due to the placement of the Br_3^- counterion.

The NMR characteristics of the bromonium ion triflate prove to be interesting in that the proton NMR spectrum of a 1:1 mixture of parent olefin and bromonium ion at room temperature is an average of those of the two isolated species. This suggests that there is a rapid site exchange of the Br^+ between the ion and olefin. The phenomenon can be most simply studied by ^{13}C NMR spectroscopy. An approximately 100 mM solution of the ion in CD_2Cl_2 held at - 80°C was treated with small aliquots of Ad=Ad, the ^{13}C NMR spectrum was monitored after each addition. At zero added Ad=Ad, the ^{13}C spectrum of the ion consists of a seven line pattern indicative of a species (eqn. 3, **5a**) having two perpendicular planes of symmetry that pass, respectively, through the three heavy atoms of the bromonium



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5a **5b**

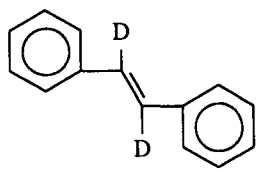
portion, and only the Br^+. $C_{8,8',10,10'}$, proximal to the Br^+, appear at 42.69 ppm while the distal carbons, $C_{4,4',9,9'}$, appear at 40.31 ppm. Addition of small aliquots of Ad=Ad causes significant broadening of these two resonances which at the fast exchange limit coalesce into a singlet at 42.02 ppm (refs. 4,5). The phenomenon is best explained by an Ad=Ad mediated translocation of the Br^+ from the topside (**5a**) to the bottomside (**5b**) of the ion which, if rapid enough, renders $C_{8,8',10,10'}$ and $C_{4,4',9,9'}$ indistinguishable. Lineshape analysis of these two resonances produces the pseudo-first order rate constant for the exchange phenomenon; a plot of the so-obtained values as a function of added [Ad=Ad] yields a straight line, the

slope of which is the second order rate constant for Ad=Ad mediated transfer of Br^+ from the top to the bottom side of the ion. Since the process depends upon [Ad=Ad], the rate-limiting step must involve an equally fast direct transfer of Br^+ between the ion and olefin. The derived rate constant of 1.0×10^6 $M^{-1}s^{-1}$ (-80°C) is remarkably fast and was shown (refs. 4,6) to have activation parameters of $\Delta H^{\neq}$ = 1.8 kcal/mol, $\Delta S^{\neq}$ = 21 cal/K/mol. The low values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ suggest that the process is not activation limited, but rather involves diffusion limited transfer with considerable restriction in the degrees of freedom of the reacting partners. From the activation parameters, the rate constant for degenerate Br^+ transfer at 25°C is $\sim 2.0 \times 10^7 M^{-1}s^{-1}$.

The above phenomenon of rapid transfer of a Br^+ from a bromonium ion to an acceptor olefin is, to our knowledge, an unprecedented one. While it may be argued that the behaviour of the Ad=Ad system is unusual or atypical in the sense that its bromonium ion is absolutely precluded by steric hindrance from proceeding to normal addition products, we see no reason why more normal olefins should not be capable of such exchange at comparable, or even greater rates than that observed here. These results indicate that intermolecular Br^+ transfer from ion to olefin must be considered as being competitive with the various product forming steps during the electrophilic bromination of olefins.

The use of secondary deuterium kinetic isotope effects in mechanistic studies of olefin bromination

Apart from a few studies (ref. 7), the use of deuterium kinetic isotope effects (kie's) appears to have had limited use in mechanistic studies of electrophilic bromination of olefins. Secondary alpha D-kie's have been reported for two cases, trans-stilbene **6** and p-substituted α-d-styrenes **7**, these giving relatively small inverse kie's of



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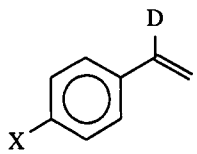

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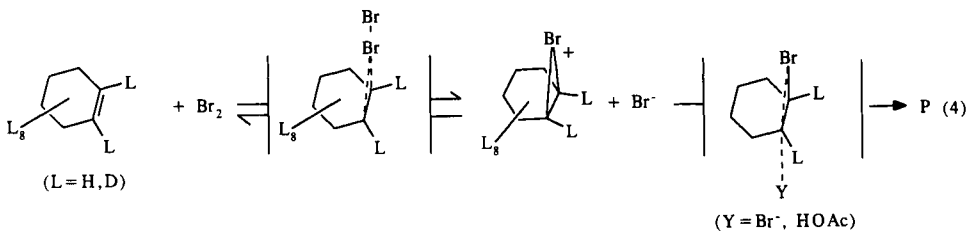
k_H/k_D = 0.91 (ref. 7a) and 0.95-0.99 (ref. 7b) respectively. The inverse nature of the secondary α-kie was explained (refs. 7a, 7b) in terms of the customary model

(ref. 8) in which the rate-limiting transition state involves rehybridization of the olefinic carbons from $sp^2 \rightarrow sp^3$. It seems reasonable to anticipate that the styrene and stilbene cases, due to the presence of the aryl ring, would proceed through asymmetric bromonium ions or possibly open β-bromocations (ref. 9). Therefore, the transition state rehybridization of the benzylic C-L (L=H,D) unit would be dampened, thereby reducing the magnitude of the isotopic substitution on the rate. Accordingly, we undertook a systematic investigation (ref. 10) of the bromination of certain deuterated cyclohexenes **2,3** in HOAc at 25°C and constant ionic strength of $\mu = 0.1$ ($LiClO_4$) with the expectation that these would proceed via symmetrical bromonium ions wherein each olefinic carbon would undergo extensive rehybridization in the t.s.

a) The Br_2 reaction

In Table 1 are the rate data for the various deuterated cyclohexenes. Control experiments established that k_{Br_2} **2a/2b** = 1.0 indicating that deuterium substitution of the four allylic positions produces no effect on the rate. The data of Table 1 show that at zero added [Br^-], k_{Br_2} **3/2a** = 1.89 (0.19). This large inverse secondary kie for the cyclohexene-d_{10} cannot be attributable to deuteration of the allylic positions (recall k_{Br_2} **2a/2b**). Likewise, substitution of the more remote homoallylic ones is also not expected to contribute greatly to the kinetics (ref. 8). Thus the large observed inverse effect must be mostly attributable to the H(D) substitution at both vinyl carbons and is consistent with a process such as in equation 4 in which considerable rehybridization of the olefinic carbons has occurred (ref. 8). Note that equation 4 contains two possible transition states that are consistent with the observed inverse kie, one leading to the intermediate bromonium ion, and the other leading away from it. It is also possible that neither t.s. is entirely rate limiting, so that the observed kie corresponds to the composite virtual transition state.



(L=H,D)

(Y=Br⁻, HOAc)

b) The Br_3^- reaction

The effect of added [Br^-] on the bromination reaction is such as to retard the rate. This phenomenon is attributable to a competing equilibrium, $Br^- + Br_2 \rightleftharpoons Br_3^-$ that decreases the available free [Br_2]. In HOAc, the accepted value for the tribromide equilibrium constant is $K_{eq} = 92\ M^{-1}$ (ref. 11). Both Br_2 and Br_3^- are brominating agents so that the rate of disappearance of total bromine, or $[Br_2]_t$, is

$$\frac{-d[Br_2]t}{dt} = k[Br_2]_t[ol] = (k_{Br_2}[Br_2]_f + k_{Br_3^-}[Br_3^-])[ol] = (k_{Br_2}[Br_2]_f + k_{Br_3^-}K_{eq}[Br^-][Br_2]_f)[ol] \quad (5)$$

where k_{Br_2} is the second order rate constant for addition of free Br_2($[Br_2]_f$), and $k_{Br_3^-}$ is the rate constant for addition of Br_3^- or its kinetic equivalent $Br^- + Br_2$. Thus, the observed global second order rate constant for disappearance of Br_2 (k_g) can be expressed (ref. 11) as

$$k_g = (k_{Br_2} + k_{Br_3^-}k_{eq}[Br^-])/(1 + K_{eq}[Br^-]) \quad (6)$$

so that a plot of $(1 + K_{eq}[Br^-])\ k_g$ vs $K_{eq}[Br^-]$ gives an intercept of k_{Br_2} and a slope of $k_{Br_3^-}$. In Figure 2 is a plot of the data of Table 1 for **2a** and **3**. The respective k_{Br_2} values are 1.08 (0.10) x 10^3 and 2.15 (0.10) x $10^3 M^{-1}s^{-1}$ while the respective $k_{Br_3^-}$ values are 3.09 (0.11) x 10^2 and 3.98 (0.11) x $10^2 M^{-1}s^{-1}$. From this treatment, the overall secondary α kie for the Br_2 addition (k_{Br_2})D/H is inverse at 2.0; the one for Br_3^- addition, ($k_{Br_3^-}$)D/H = 1.29, is somewhat less inverse and can be analyzed in the following way.

Table 1. Rate Constants for Bromination of **2a** and **3** in HOAc as a Function of Added [Br^-]; T=25°C, μ=0.1 ($LiClO_4$)[a]

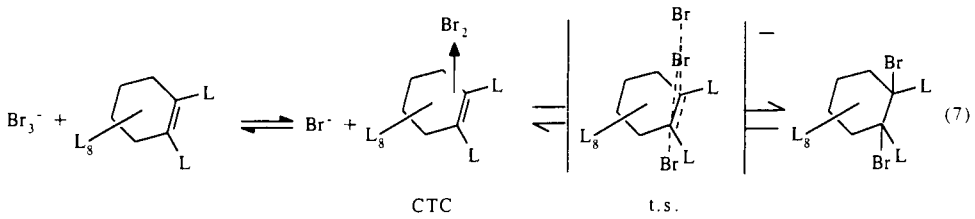
Olefin	LiBr(M)	$LiClO_4$(M)	$k_g(M^{-1}s^{-1})$[b]
2a	0	0.1	1.18×10^3
3	0	0.1	2.10×10^3
2a	0.025	0.075	5.16×10^2
3	0.025	0.075	9.75×10^2
2a	0.05	0.05	4.30×10^2
3	0.05	0.05	6.92×10^2
2a	0.075	0.025	4.12×10^2
3	0.075	0.025	6.12×10^2
2a	0.1	0	3.88×10^2
3	0.1	0	5.76×10^2

a. $[Br_2]$ = 1-2 x 10^{-4} M; [ol] = 2 x 10^{-3} M; followed at 410-480 nm

b. k_g defined as k_{obsd} / [ol]; see text

There are three often cited possibilities for the Br_3^- reaction (ref. 11) : these are (a) a salt effect that influences the polarity of the medium and hence its ability to support charge developing in the t.s., (b) Br_3^- acting as an electrophile to yield a bromonium ion and two Br^-, and, (c) a kinetically equivalent nucleophilic reaction similar to that discussed by Yates (ref. 11d), Bellucci (ref. 12) and others (ref. 11e,f) where Br^- captures the CTC or some other intermediate having the same stoichiometry (e.g., a bromonium ion/Br^- ion pair). We have earlier discussed the extant data as it pertains to the three above possibilities (ref. 10), but the secondary kie valued shed new light on the Br_3^- reaction. With respect to the mechanistic possibilities above, the expected kie's are (a) $k_{Br_3^-}$ **3/2a** = 1.0 and insensitive to ionic strength effects (b); $k_{Br_3^-}$ **3/2a** is large, perhaps 2.0, for Br_3^- acting as an electrophile since the t.s. would be similar, in terms of rehybridization of the olefinic cations, to the t.s. for the Br_2 reaction, and (c) $k_{Br_3^-}$ **3/2a** is significantly smaller than that for the Br_2 reaction if Br^- captures the CRC since this would involve not only an asymmetric transition state, but also one having far less rehybridization of the olefinic carbons. That the observed value of $k_{Br_3^-}$ **3/2a** = 1.29 is significantly smaller than that for the Br_2 reaction indicates that the respective transition states are dissimilar. The low value supports Br^- capture of the CTC or its kinetic equivalent (eqn 7). In effect, the process has a strong similarity to nucleophilic substitution reactions (S_N2 or N_DI) which are known to exhibit low

secondary α kie's, particularly in the case of neighboring group participations (ref. 13).



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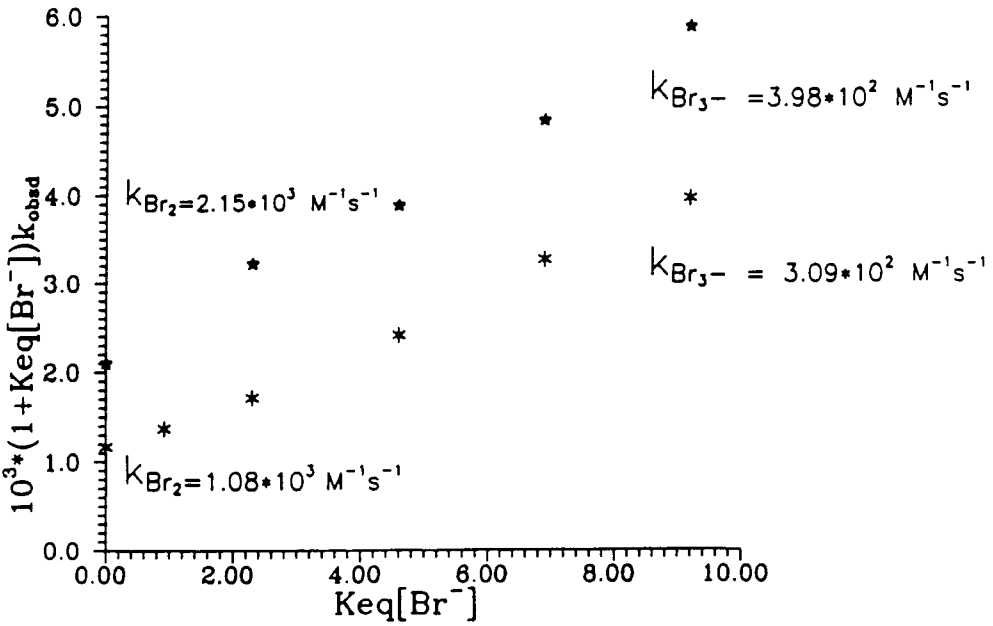


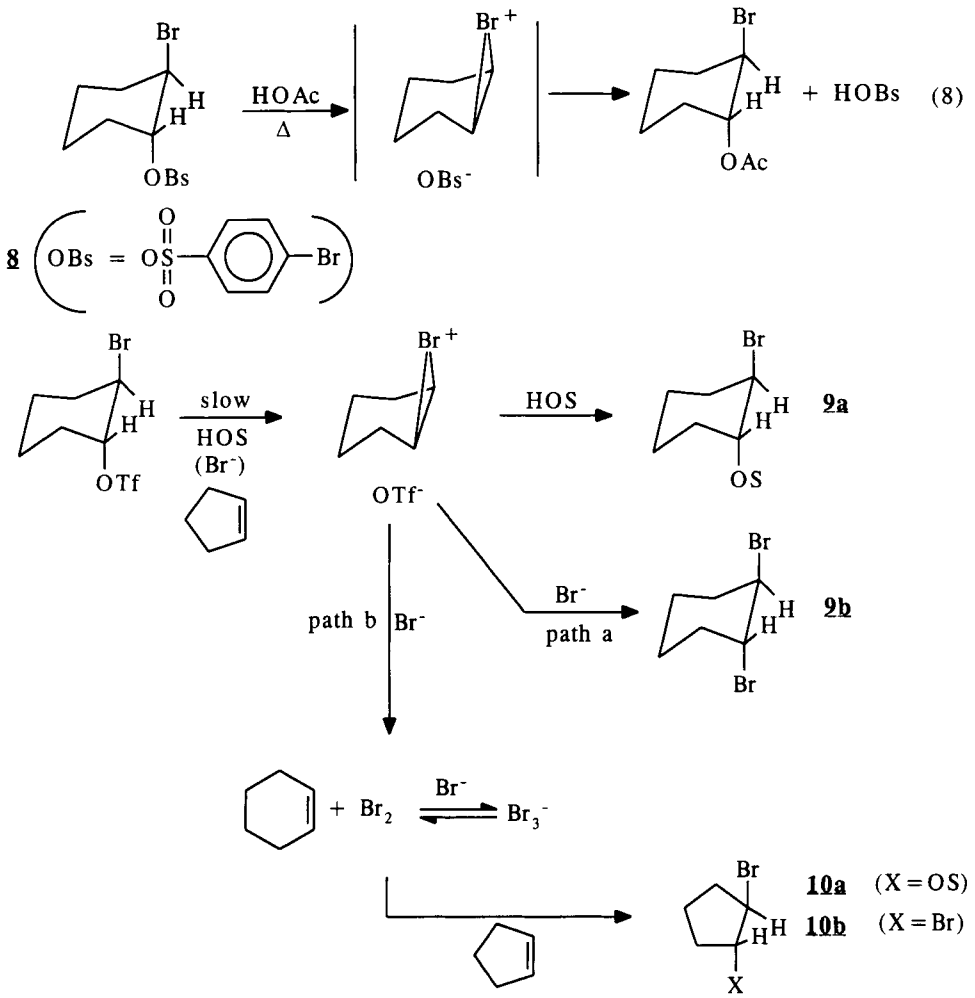
Figure 2. A plot of kg (1 + K_{eq} [Br^-]) vs K_{eq} [Br^-] for bromination of cyclohexene (*) and cyclohexene-d_{10} (★) in HOAc at T = 25°C, μ=0.1 ($LiClO_4$)

What we have shown here is the fact that large inverse values can be obtained for the Br_2 addition to a "normal" olefin which should pass through a symmetrical, or nearly so, transition state. Of course, more work involving other systems would be beneficial in assessing the scope and limitation of the use of the α-deuterium kie's in mechanistic studies of Br_2 and Br_3^- reactions with olefins.

The Solvolysis of *trans*-2-bromocyclohexanetrifluoromethanesulfonate 4 in the presence of Br^- Generates Cyclohexene and Free Br_2

A classical approach to assessing the behavior of ions or intermediates suspected to be present during a given reaction is to generate those ions in a completely different way, and to then study their fates under conditions relevant to the original reaction in question. With respect to Br_2 addition to olefins, it is difficult to tell whether the proposed intermediate bromonium ion is formed reversibly (e.g., eqn. 1). This is because even if the ion reacts reversibly with Br^-, this simply reforms the starting materials, the ultimate fate of which is to progress through the reaction manifold to form products. However, in principle, if a *bona fide* bromonium ion could be generated independently, and if this were shown to be capable of reacting with Br^- to form Br_2, then at least phenomenologically, one would have evidence that Br^- was capable of attacking a bromonium ion on Br^+ in competition with the normal process of C-attack to form dibromide products.

In what is now a classic series of papers concerning neighboring group participation, Winstein and coworkers (ref. 14) showed that *trans*-2-bromocyclohexane-p-bromobenzenesulfonates 8 solvolyzed in HOAc with the involvement of the trans Br through the intermediacy of a transient bromonium ion (eqn 8). Our approach (ref. 15) to the reversibility problem involved solvolysis of the corresponding 2-bromocyclohexanetrifluoromethanesulfonate 4, (a far more reactive material) in HOAc or MeOH at ambient temperature in the absence and presence of added Br^- and a reactive scavenger olefin, cyclopentene. The overall approach is shown in Scheme 1. Solvolysis of 4 should proceed with the neighboring group assistance through the bromonium ion which, after capture by solvent, gives the corresponding



Scheme 1. Solvolysis of *trans*-2-bromotriflate of cyclohexane in the presence of Br^- and a scavenger olefin, cyclopentene.

trans-2-bromosolvate **9a**. Added Br^- introduces two new fates. The first, labelled path a in Scheme 1, is simple capture of the ion at C to produce the trans dibromide **9b**. Alternatively, as in path b, capture at Br^+ generates cyclohexene and Br_2, but the latter, in the absence of scavengers would simply read to the nascent cyclohexene to again give **9a,b**. However, in the presence of added cyclopentene, the so-produced Br_2 rapidly reacts to give **10a,b**. Thus, quantitative measure of the amount of **10a,b** and **9b** gives an exact measure of the partitioning of the bromonium ion between Br^- capture on Br^+, or on C.

Given in Tables 2 and 3 are the observed product distributions for the solvolyses conducted at varying [Br-]. Several points are evident from the data. First, no cyclopentyl products are observed in the absence of added Br^-. This indicates that under the solvolysis conditions, Br^+ transfer from the cyclohexyl bromonium ion to cyclopentene is not important; otherwise the trans 2-bromosolvates of cyclopentene would be observed. Second, as judged from the ratio of (**10b** + **10a**)/**9b** given in Tables 2 and 3, when Br^- is present, more cyclopentyl products are observed than cyclohexyl dibromide. This indicates that Br^- capture of the bromonium ion on Br^+ to form Br_2 is more prevalent than is Br^- attack on C. Third, in all cases only trans products were observed : this provides strong evidence for the intermediacy of the solvolytically produced bromonium ion, otherwise cis products would be observed. Fourth, the fact that the ratio of the cyclopentyl products to dibromocyclohexene is essentially invariant to [Br^-] (ref. 16) provides valuable confirmatory evidence that these three species arise from Br^- attack on a common intermediate that we take to be the bromonium of cyclohexene. If Br^- were involved in promoting the elimination of Br^+/OTf^- from **4** the ratio of the cyclopentyl products (**10a** + **10b**) to **9b** would increase markedly as a function of added Br^-.

Two main control experiments establish that a) free Br_2 is generated during the course of the above solvolysis, and b) Br^- is not involved in any rate limiting step of the solvolysis. If free Br_2 was generated from **4** + Br^-; then its addition to cyclopentene should proceed to yield **10a** and **10b** in a ratio that is identical to that observed for the addition of authentic Br_2 under the same conditions. Br_2 addition to cyclopentene in HOAc containing 0.1 M LiBr gives a ratio of **10b**/**10a** (OS=OAc) of 12.3; from Table 2, solvolysis of **4** at 0.1 M LiBr gives a **10b**/**10a** (OS=OAc) ratio of 12.0-12.6. Similar controls with Br_2 addition to cyclopentene in MeOH containing 0.1 and 0.3 M Br^- indicate the respective ratios of **10b**/**10a** ($OS=OCH_3$) are 0.38 and 1.2; solvolysis of **4** under similar conditions gives ratios of 0.33 and 1.1.

Table 2. Percentages of Dibromocyclohexane **9b**, Dibromocyclopentanone **10b**, trans-1-Acetoxy-2-bromocyclohexane **9a**, (OS=OAc) and trans-1-Acetoxy-2-bromo-cyclopentane **10a** (OS=OAc) obtained from Solvolysis of **4** in HOAc containing 0.5 M Cyclopentene and Varying [Br^-], μ=0.1($LiClO_4$),[a]

[LiBr] (M)	% **10b**	% **10a** (OS=OAc)	% **9b**	% **9a** (OS=OAc)	(**10b**+**10a**)/**9b**
0.0	0	0	0	100	--
0.025	9.7	3.1	5.4	81.7	2.4
0.05	17.4	3.7	8.4	70.5	2.5
0.75	22.4	3.2	10.8	63.6	2.4
0.10	26.4	2.2	12.8	58.7	2.2

a. Ambient temperature (22-26°C); [**4**] = 0.015 M; Averages of triplicate determinations; estimated error ± 0.4 %.

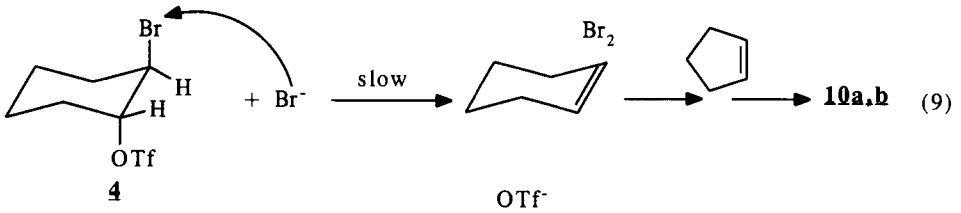
Table 3. Percentages of Dibromocyclohexane **9b**, Dibromocyclopentane **10b**, trans-1-Methoxy-2-bromocyclohexane **9a**, (OS=OCH_3) and trans-1-Methoxy-2-bromo-cyclopentane **10a**, (OS=OCH_3) obtained from Solvolysis of **4** in MeOH containing 0.5 M Cyclopentene and Varying [Br^-], μ= 0.3($LiClO_4$),[a]

[LiBr] (M)	% **10b**	% **10a** (OS=OCH_3)	% **9b**	% **9a** (OS=OCH_3)	(**10b**+**10a**)/**9b**[b]
0.0	0	0	0	100	--
0.1	3.2	9.7	1.2	84.9	10.8±4.2
0.2	9.9	14.2	2.0	73.0	12.0±2.5
0.3	18.9	17.2	2.5	60.5	14.4±2.2

a. Ambient temperature (22-26°C); [**4**] = 0.015 M; Averages of duplicate determinations; estimated error ± 0.3 %.

b. Errors computed from estimated errors in **10b**, **9b**, **10a**.

Second, while the above experiments indicate the presence of free Br_2 during the solvolysis, they do not indicate how it was produced. One possibility tested for is shown in equation 9,



where Br^- nucleophilically promotes the Br^+/OTf^- elimination to generate free Br_2 and cyclohexene. This process requires that the rate of solvolysis of **4** be linearly dependent on [Br^-]. However, control (ref. 15) kinetics experiments indicate that the rate constant for solvolysis of **4** in HOAc or MeOH are independent of Br^- : thus generation of free Br_2 must occur after the rate limiting step. This nicely confirms the previous conclusion based upon the invariance of the (**10a**+**10b**)/**9b** ratio on [Br^-].

All the above solvolysis data are rationalized by the process depicted in Scheme 1. What is important for our consideration here is that a solvolytically produced bromonium ion of a "normal" olefin has been shown to react in both MeOH and HOAc by preferential attack of Br^- on Br^+. This simple set of experiments might be taken as indicating bromonium ion reversal during electrophilic addition of Br_2 to olefins is more prevalent than was originally believed.

Acknowledgements

The author expresses his gratitude to the Natural Sciences and Engineering Research Council of Canada for its continued support of his research. He also acknowledges the talented group of researchers whose names appear on the publications from his laboratories.

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6. k_{obsd} (s^{-1})T, °C; 200 (-103.1°); 350 (-90.9°);450 (-80.6°); 650 (-70.9°); 800 (-60.3°); 900 (-51.3°).
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16. That the ratio of **10a** ($OS{=}OCH_3$) + **10b**/**9b** varies from 10.8 to 14.4, we believe, is due to the relatively small amount of **9b** produced (Table 3, 0-2.5 %). Given the uncertainty of ±0.3 % on these small numbers, the reported ratios are experimentally the same.

NEW MECHANISTIC INSIGHT INTO THE ELECTROPHILIC BROMINATION OF OLEFINS

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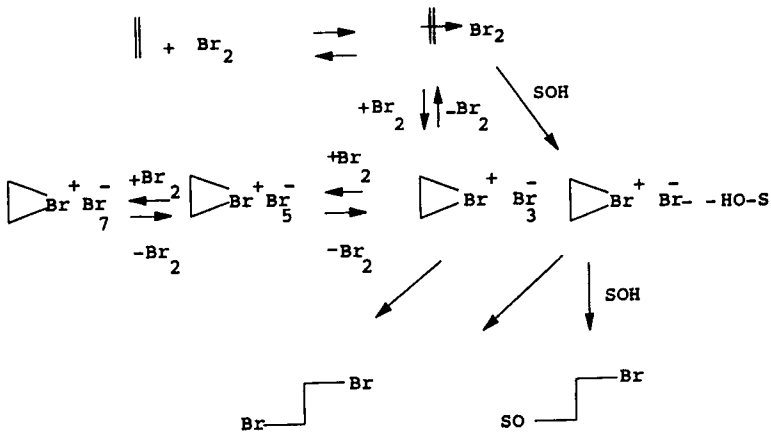
This paper is concerned with the most recent advances in the understanding of the mechanism of electrophilic olefin bromination. This seemingly simple reaction is undoubtedly the most common example of a reaction typical of unsaturated systems presented in organic chemistry textbooks. It has been subjected to extensive investigation in the past few decades (ref. 1).These investigations have brought to light a complicated picture involving a number of mechanistic variations. Few crucial points remain, however, to be conclusively defined, and will be discussed in this paper.

Excluding free radical bromination processes, a schematic picture of the mechanistic pathways involved in olefin bromination is shown in Scheme 1.



Scheme 1. Mechanistic pathways involved in olefin bromination

Formation and role of olefin-Br_2 charge transfer complexes

First of all, the reaction pathways shown in Scheme 1 involve the formation of charge transfer complexes (CTC) between olefin and Br_2. The formation of molecular complexes during olefin bromination had been hypothesized often (ref. 2), but until 1985, when we published a work on this subject (ref. 3), complexes of this type had been observed only in a very limited number of circumstances, all of which have in common a highly reduced reactivity of the olefin-halogen system, i.e. strongly deactivated olefins (ref. 4), or completely apolar solvents (ref. 5) or very low temperatures (ref. 6).

No direct detection of CTC's had instead been reported for fast reacting systems of olefins and Br_2 in solvents of moderate or high polarity, where the existence and the kinetic role of these complexes had been only a matter of speculation.

We were able to observe the formation of CTC's between cyclohexene and Br_2 in 1,2-dichloroethane (DCE), where the rate of bromination is very high and obeys a third-order rate law (eqn. 1), by using the stopped flow technique (ref. 3). The UV-Vis absorption spectrum of this species exhibited its λ_{max} at 287 nm. Its formation constant K_f was found at three different temperatures using initial absorbance values of solutions containing variable, high olefin excesses and low bromine concentrations. Initial, rough evaluations of K_f values were obtained using the Scott equation (ref. 7). These values were then refined by a non-linear least-squares (NLLSQ) fitting procedure, that also gave the molar extinction coefficients of the CTC. Relevant data are reported in Table 1. A fitting of K_f against 1/T gave a negative ΔH = - 4.60 (0.2) kcal mol^{-1} and a negative ΔS = - 17 (0.6) eu. The third-order rate constants (k_3) for the bromination of cyclohexene at the same three temperatures were measured (Table 2) and a negative apparent activation energy $E_{a(obsd)}$ = - 7.8 (0.3) kcal mol^{-1} was obtained.

$$-d[Br_2] / dt = k_3 [Br_2]^2[Ol] \qquad (1)$$

Table 1 : Formation Constants and Molar Absorptivities at 287 nm of the 1:1 Cyclohexene-Br_2 CTC Obtained from Initial Absorbances of Mixtures of Bromine and Cyclohexene in 1,2-Dichloroethane [a].

T °C	K_f M^{-1}	ε CT M^{-1} cm^{-1}
15	0.60 (0.07)	5640 (545)
25	0.47 (0.08)	5520 (271)
35	0.37 (0.05)	5375 (585)

[a] From ref. 3.

Table 2 : Third-order Rate Constants for the Bromination of Cyclohexene in 1,2-Dichloroethane [a]

T °C	10^{-5} k_3 M^{-2} s^{-1}
15	3.84 (0.21)
25	2.40 (0.11)
35	1.59 (0.05

[a] From ref. 3.

Of course the observation of olefin-Br_2 CTCs in solutions of olefins and Br_2 does not necessarily mean that these are essential intermediates in olefin bromination. However the above thermodynamic and kinetic parameters allowed us to answer the question of the mechanistic role played by the CTCs. In fact, if they were unreactive species whose only effect is to reduce the concentration of the actual reactants, Scheme 2 would be valid. The observed k_3 would be given by

$$Ol + Br_2 \overset{K_f}{\rightleftharpoons} CTC$$

$$Ol + 2\,Br_2 \xrightarrow{k_3} \text{dibromide} + Br_2$$

$$-d[Br_2]_{tot} / dt = k_3\,[Br_2]^2_{free}\,[Ol]$$

$$[CTC] = K_f\,[Br_2]_{free}\,[Ol]$$

$$[Br_2]_{tot} = [Br_2]_{free} + [CTC] = (1 + K_f\,[Ol])\,[Br_2]_{free}$$

$$-d[Br_2]_{free} / dt = k_{3\,(obsd)}\,[Br_2]^2_{free}\,[Ol]$$

$$k_{3\,(obsd)} = k_3 / (1 + K_f\,[Ol]) \qquad (2)$$

$$E_{a\,(obsd)} = E_{a\,(3)} - \Delta H\,(K_f\,[Ol] / (1 + K_f\,[Ol]))\ ) \qquad (3)$$

Scheme 2.

equation (2) and the apparent activation energy $E_{a(obsd)}$ would be given by equation (3), where $E_{a(3)}$ represents the real activation energy for a termolecular process, and is necessarily positive. Because ΔH for the CTC formation has been

found to be negative, also the $E_{a\ (obsd)}$ must be positive. Since this is not the case, it can be concluded that Scheme 2 does not fit the kinetic-thermodynamic data.

If the CTC's are instead the reactive intermediates of the bromination, Scheme 3 is valid. The observed rate constant is given by eq (4) and $E_{a\ (obsd)}$ is given by equation (5). If ΔH is negative this equation can give a negative value of $E_{a\ (obsd)}$, as actually found, provided that $|\Delta H|$ is larger than the true activation energy for the CTC ionization, $E_{a(2)}$, and $K_f\,[Ol] < |\Delta H| / E_{a(2)}$, that is for reactions carried out at not too low temperatures (or high K_f) and not too high olefin concentrations.

$$Ol + Br_2 \underset{}{\overset{K_f}{\rightleftharpoons}} CTC$$

$$CTC + Br_2 \xrightarrow{k_2} \text{dibromide} + Br_2$$

$$-d[Br_2]_{tot}/dt = k_2\,[CTC]\,[Br_2]free$$

$$k_{3\ (obsd)} = k_2\,K_f / (1 + K_f\,[Ol])) \qquad (4)$$

$$E_{a\ (obsd)} = E_{a\ (2)} + \Delta H\,(1 / (1 + K_f\,[Ol])) \qquad (5)$$

Scheme 3.

In conclusion, only Scheme 3 matches the kinetic and thermodynamic data, showing that the CTC's are essential intermediates of the bromination reaction.

Next step was to try to determine K_f values for other olefin-Br_2 CTC's in order to check the structural effects on their stabilities.

Figure 1 shows the UV-Vis spectra of DCE solutions of 5H-dibenz[b,f]azepine-5-carbonyl chloride and Br_2 (ref. 8) (Fig. 1).

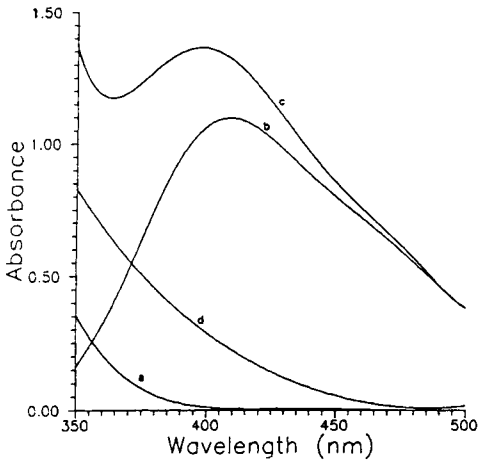


Fig. 1. UV-vis spectra of 5 x 10^{-1} M 5H-dibenz[b,f]azepine-5-carbonyl chloride, (a), 5 x 10^{-3} M Br_2, (b), 5 x 10^{-1} M olefin and 5 x 10^{-3} M Br_2, (c), in, 1,2-dichloroethane at 25°C, and the difference between (c) and (a+b), (d).

This olefin was chosen because its slow bromination rate allows to make accurate measurements of transient CTC's with a conventional spectrophotometer. Curve *d* is a difference spectrum between a solution of Br_2 plus a hundred fold excess of olefin (curve *c*) and those of the single reagents (curves *a* and *b*), and represents the tail of the expected CT band. From the linearity of the plots of the difference absorbance agains the olefin concentration (Fig. 2) it was possible to evaluate a limiting value of $Kf < 0.1$ M^{-1}. On the other hand, a $\Delta H = -0.9$ kcal mol^{-1} was obtained from a plot (Fig. 3) of the in of the products $K_f\varepsilon_{CT}$, obtained from the first plot, against 1/T, assuming ε_{CT} to be temperature independent (ref. 3).

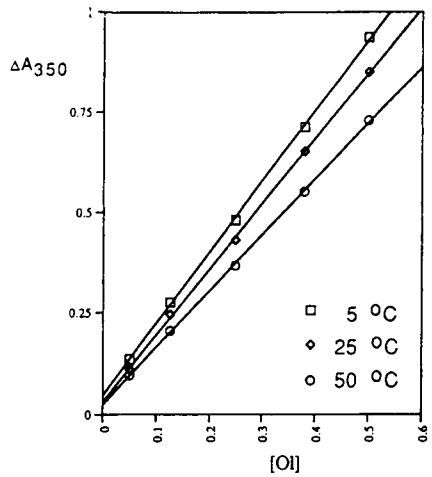


Fig. 2. Plots of the difference absorbance at 350 nm against the concentration of 5H-dibenz[b,f]azepine-5-carbonyl chloride for 5.2 x 10^{-3} M Br_2 and 5 x 10^{-2} to 5 x 10^{-1} M olefin in 1,2-dichloroethane at 5,25 and 50°C.

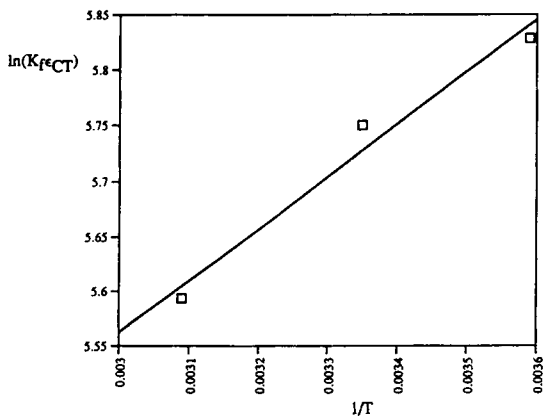


Fig. 3. Fit of ln($K_f\varepsilon$CT) against 1/T obtained in 1,2-dichloroethane at 5,25 and 50°C for the 5H-dibenz[b,f]azepine-5-carbonyl chloride-Br_2 CTC.

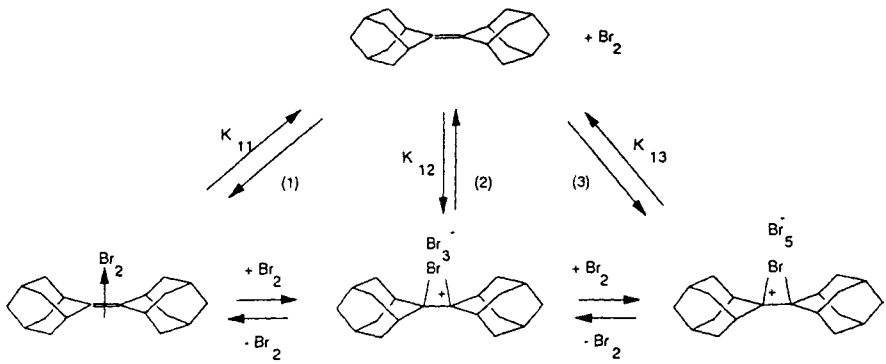
Normal tetrasubstituted olefins react with Br_2 too fast to allow the observation of transient CTC's. We therefore chose an encumbered olefin, tetraisobutylethylene, in order to slow down the reaction rate (ref. 9). A large number of initial absorbances were measured for solutions of different olefin and Br_2 concentrations with the stopped-flow technique in the 250 - 500 nm interval at three temperatures between 6 and 50°C, and submitted to a NLLSQ fitting procedure. A 9.71 (0.19) M^{-1} value was found for the K_f at 25°C, with a ΔH of - 4.07 kcal mol^{-1} and a ΔS of - 9.2 eu. We also were able to measure the K_f values for the same CTC in two protic solvents, acetic acid and methanol. In both cases a value of around 2 M^{-1} was obtained, showing an unimportant influence of protic solvents on K_f (Table 3).

Table 3 : Solvent and Temperature Dependence of the 1:1 Formation Constants of Tetraisobutylethylene-Br_2 CTC. [a]

Solvent	T, °C	K_f M^{-1}
DCE	25	9.71 (0.19)
DCE	50	5.80 (0.24)
DCE	6	16.07 (1.05)
acetic acid	25	1.72 (0.20)
methanol	25	≈ 2.5

[a] From ref. 9.

We passed then to a particular olefin, adamantylideneadamantane, whose reaction with Br_2 had been shown to stop at the stage of bromonium ion formation because of steric hindrance to backside nucleophilic attack. An UV-Vis spectrophotometric study (ref. 10) has shown that the complicated equilibrium reported in Scheme 4 is immediately established on mixing the olefin and Br_2 in DCE. Equilibrium (1) could be isolated by working at low Br_2 and ten to hundred fold higher olefin concentrations. A Scott plot followed by a NLLSQ refinement of the data gave a $K_f = 2.89 \times 10^2$ (4.0) M^{-1}. It is worth noting that conductimetric measurements showed the non-ionic nature of the 1:1 adduct, consistent with a CTC intermediate, but not with a bromonium-bromide species.



Scheme 4. Bromination of adamantylideneadamantane.

It was argued (ref. 11) that adamantylideneadamantane is a particular olefin, in that it is unable to give the dibromide product. We chose therefore to investigate an other cage olefin, *d,l*-D_3-trishomocubylidene-D_3-trishomocubane, having a structure similar to adamantylideneadamantane, but being brominated fast to the expected dibromide (ref. 12). Figure 4 reports the initial absorbances taken with the stopped-flow technique at constant Br_2 and increasing olefin concentration. The curve is consistent with a progressive complexation of Br_2 by the olefin to give a 1:1 CTC. Fitting these data to the Scott equation followed by refinement with the usual NLLSQ procedure gave a K_f = 7.68 (0.65) x 10^2 M^{-1}.

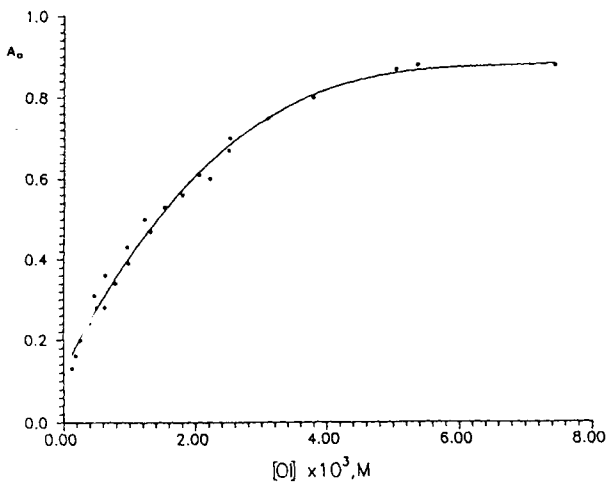
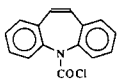
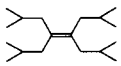


Fig. 4. Initial absorbances (A_0) in 2 cm cell at 300 of mixtures of 1.6 x 10^{-4} M to 7.5 x 10^{-3} M *dl*-D_3-trishomocubyidene-D_3-trishomocubane and 1.6 x 10^{-4} M Br_2 in 1,2 dichloroethane at 25°C against the olefin concentrations.

In Table 4, the spectral and thermodynamic parameters of the five investigated CTC's in DCE are summarized. It can be observed that the K_f are spread over at least 3-4 orders of magnitude.

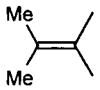
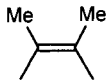
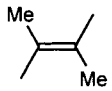
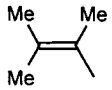
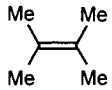
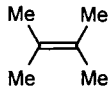
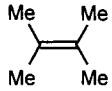
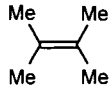
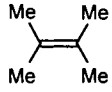
Table 4 : Structural Effects on 1:1 CTC Formation Constants (K_f) Between Br_2 and Olefins and the Respective Bromination Rates.

Olefin	λ_{max}	ε_{max} (M^{-1} cm^{-1})	K_f (M^{-1})	ΔH (kcal mol^{-1})	ΔS (eu)	k_3 (M^{-2} s^{-1})
	287	5520 (271)	0.47 (0.08)	-4.60 (0.20)	-17.0 (0.6)	2.4 (0.1)x10^5
			< 0.1	-0.9 (0.05)		1.5 (0.1)x10^{-2}
	260	4963 (19)	9.71 (0.19)	-4.07 (0.35)	-9.20 (0.11)	7.7 (0.1)x10^{-1}a
	272	18224 (16)	2.89 (0.4) x 10^2			
	267	9100 (100)	7.68 (0.85) x 10^2			3.0 (0.5)x10^5 b

a Second order rate constant (k_2) measured in acetic acid and espressed in M^{-1} s^{-1}.
b Second order rate constant (k_2) for the disappearance of the CTC, espressed in M^{-1} s^{-1}.

In similarly substituted olefins K_f is strongly influenced by steric effects, as shown by the comparison of tetraisobutylethylene with adamantylideneadamantane and *d,l*-D_3-trishomocubylidene-D_3-trishomocubane. In particular, the comparison between cyclohexene and the two tetrasubstituted cage olefins indicates that K_f increases at least by a factor of 10^3 on passing from a 1,2 disubstituted to a tetrasubstituted olefin. This dependence is likely to be similar in other solvents, because solvent effects on K_f are modest.

Table 5 : Rate Ratios for the Bromination of Ethylenes.

Olefins		Rate ratios	Solvent
		8.0×10^3	MeOH [a]
		5.1×10^3	MeOH [a]
		2.8×10^3	MeOH [a]
		3.2×10^3 3.8×10^3	MeOH [b] AcOH [b]
		2.9×10^2 4.6×10^2	MeOH [b] AcOH [b]
		6.1×10^2 5.7×10^2	MeOH [b] AcOH [b]
		1.1×10^3 7.5×10^2	MeOH [b] AcOH [b]
		2.6×10^2	EtOH [b]
		4.1×10^2	EtOH [b]

[a] Data from : M.-F. Ruasse, A. Argile, Bienvenue-Goetz, J.-E. Dubois, J. Org. Chem., 44, 2758, (1979).

[b] M.-F. Ruasse, B.-L. Zhang, J. Org. Chem., 49, 3207, (1984).

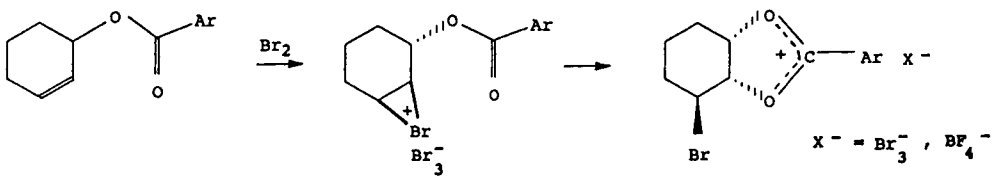
Table 5 shows the rate ratios between ethylenes differing by an increase by two in number of alkyl substituents. It can be observed that in solvents as different as methanol, ethanol, and acetic acid, the rate ratio is always around 10^3, that is of the same order of magnitude of the increase in K_f. This indicates that substituent effects are not much more influential on the kinetic constants that on K_f. A possible rationalization of the lower accelerating effects by alkyl substituents on the bromination rate, relative to what could be expected for an Ad_EC1 mechanism on

the basis of their effects on K_f, could be found in a reversible ionization of CTC's to bromonium bromide ion pairs.

Formation of bromonium-(or bromocarbonium-) polybromide ion pairs

The second step of the bromination reaction in aprotic chlorinated solvents consists of the ionization of the CTC's, and leads to bromonium or bromocarbonium tribromide ion pairs. A direct evidence for the formation of bromonium-tribromide pairs is the isolation and X-ray structural characterization of the adamantylideneadamantane-bromonium tribromide species, obtained by Brown (ref. 13).

A less direct but significant evidence for the formation of ionic intermediates also in the case of reactive olefins is given by the isolation of a 2-aryl-1,3-dioxolan-2-ylium ion as Br_3^- salt, that has been crystallized as BF_4^- salt, during the bromination of cyclohexenol benzoates (Scheme 5) (ref. 14). Clearly this salt derives from a first formed bromonium tribromide intermediate by nucleophilic attack by the carbonyl oxygen of the ester group. It must be underlined that this salt was isolated in carbon tetrachloride, showing that even in this non-polar, aprotic solvent the electrophilic bromination is an ionic process, at variance with a direct rearrangement of a 1:2 olefin-Br_2 complex through a non polar six-membered transition state, previously proposed by russian authors (ref. 15).



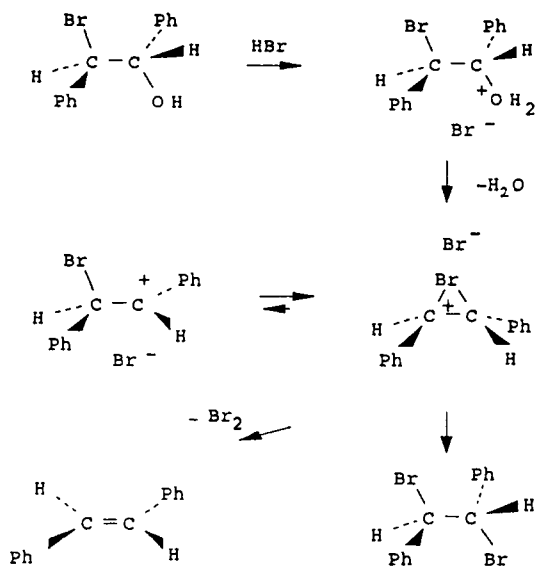
Scheme 5. Bromination of cyclohexenol benzoates.

Furthermore, a well detectable conductivity has been measured in solutions of Br_2 and certain olefins, like carbamazepine, pointing to the accumulation of ionic intermediates during the bromination process (ref. 16).

Reversibility of bromonium ion formation

In Scheme 1 the ionization of CTC's to bromonium-polybromide ion pairs is indicated as a reversible process. The first evidence for reversibility of bromonium ion formation was produced by Brown in 1984 (ref. 17). The basic idea was to generate the cyclohexene and cyclopentene bromonium ions by solvolysis of the corresponding trans bromohydrins brosylates is hot acetic acid containing bromide ions and a scavenger olefin. Small amounts of crossed dibromides and acetoxy bromides were obtained, showing that Br^- was able to attack at the bromonium bromine to give the corresponding olefin and free Br_2, which is captured by the scavenger olefin. Recently, the same author has been able to produce more convincing evidence for the reversibility of a cyclohexene bromonium ion obtained by a similar solvolytic process, but under milder conditions both in acetic acid and methanol (ref. 18).

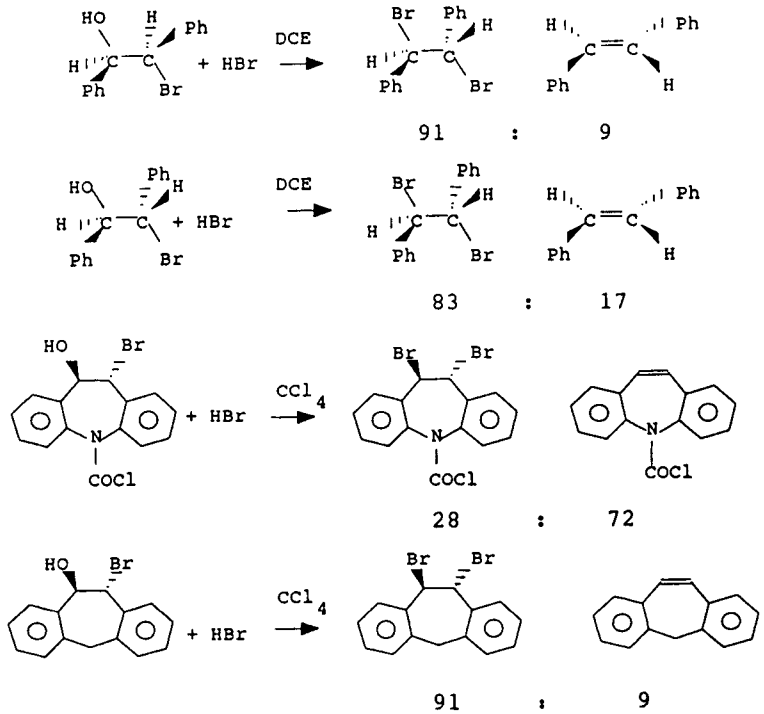
We used a similar approach in aprotic solvents and produced bromonium-bromide type intermediates by reacting stilbene bromohydrins with hydrogen bromide using a vigorous stream of the gaseous reagent to strip the Br_2 generated by attack of Br^- to Br^+ of the bromonium ion, as shown is Scheme 6 for *erythro*-2-bromo-1,2-diphenylethanol.



Scheme 6. Reaction of stilbene bromohydrin with hydrogen bromide

Relevant results are included in Table 6, showing that the *meso* dibromide and *trans*-stilbene are formed in ratios ranging between 9 to 1 and 8 to 2 (ref. 19).

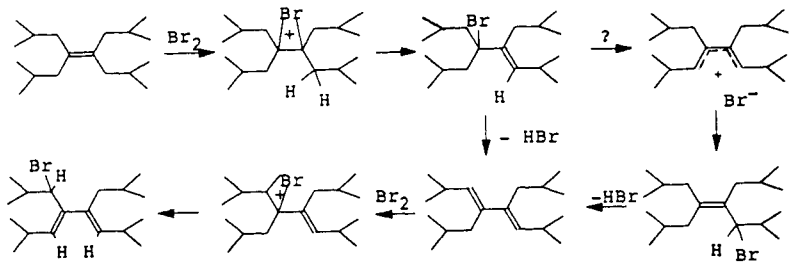
Table 6 : Ratios of Dibromides to Olefins in the Reactions of Bromohydrins with Gaseous HBr.



Other examples are given by the reaction of *trans*-10-bromo-10,11-dihydro-11-hydroxy-5H-dibenz[b,f]azepine-5-carbonyl chloride with gaseous HBr in CCl_4 to give the expected trans dibromide and the corresponding olefin in an about 3:7 ratio (Table 6) (ref. 20). The same reaction of *trans*-10-bromo-10,11-dihydro-11-hydroxy-5H-dibenzo[a,d]cycloheptene gives the dibromide and the olefin in a 9:1 ratio, similar to that obtained with stilbene bromohydrins (Table 6) (ref. 21). The much higher tendency to elimination in the dibenzoazepine derivative has been attributed to angle strain in the dibromide (shown by X-ray structure determination) (ref. 20) and to the strongly bridged bromonium ion nature of the intermediate, in comparison with the weakly bridged nature of the ions derived from stilbene and dibenzocycloheptene (ref. 21).

A kinetic evidence for reversibility of bromonium ion formation has been obtained in the reaction of tetraisobutylethylene and its D_8 labeled derivative with Br_2 in acetic acid (ref. 9). Owing to steric effects, the first formed bromonium ion cannot undergo backside attack to give the dibromide, but looses a proton to yield

an allylic bromide, which then undergoes further slow transformations to diene and other coloured products (Scheme 7). A large primary KIE k_H/k_D of 2.3 was found for the reaction leading to the allylic bromide, indicating that an allylic CH or CD bond is broken in a rate limiting or partially rate limiting step. This requires that all steps preceding the rate limiting one must have lower activation energies, so that the bromonium ion intermediate must be reversible formed.



Scheme 7.

Quantitative information about the equilibrium between olefin and Br_2 on the one hand and CTC's and bromonium ion species on the other (Scheme 4) has been obtained by the already mentioned UV-Vis spectrophotometric study of the adamantylideneadamantane Br_2 system (ref. 10). The spectrophotometric UV-Vis data of a large set of solutions of different reagents concentrations have been used to dissect, using a program based on NLLSQ fitting procedures, the complex spectra in those of the single species present at the equilibrium, as shown in Figure 5.

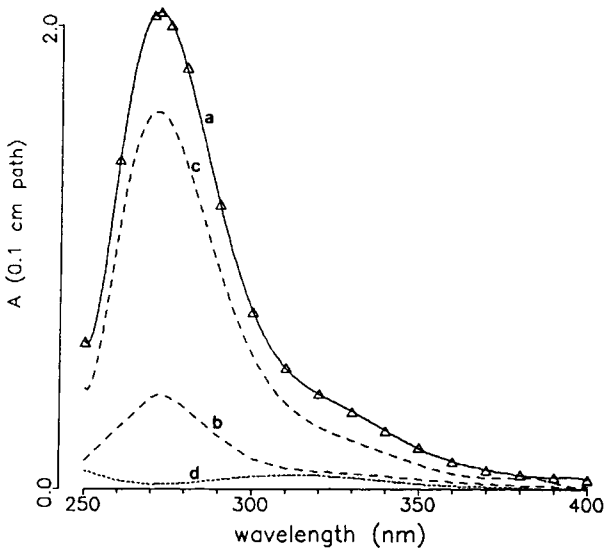
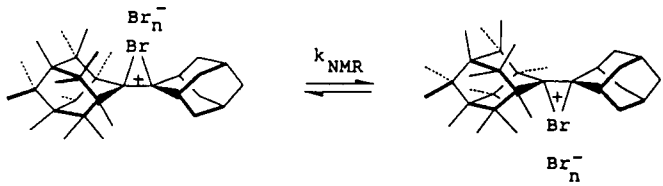


Fig. 5. Experimental (a) and calculated (Δ) spectrum at 25°C of a 1,2-dichloroethane solution of adamantylideneadamantane and Br_2 at respective 1.13 x 10^{-3} M and 2.30 x 10^{-3} M analytical concentrations. The calculated spectrum is the sum of the computed single spectra of all species presented at the equilibrium. The contributing spectra of CTC (b), bromonium tribromide (c), and brominium pentabromide (d) are also reported.

Both the CTC and the bromonium tribromide species have their λ_{max} at 272 nm, but with very different ε. Furthermore, at the employed Br_2 concentrations the counteranion of the bromonium ion is partitioned between Br_3^- and Br_5^-, the latter having its λ_{max} batochromically shifted at 310 nm. The equilibrium constant between the tribromide and the pentabromide species of Scheme 4 is 22.3 M^{-1}, that is nearly coincident with that found for the tetrabutylammonium tribromide-pentabromide equilibrium (ref. 22).

Further information concerning the reversible formation of bromonium ion-polybromide pairs came from a DNMR study of the adamantylideneadamantane Br_2 system (ref. 23). The observed phenomenon is shown in Scheme 8. In the fast exchange limit the spectrum between 2.1 and 2.6 ppm is the one reported in the upper part of Figure 6, and reveals three orthogonal symmetry planes equivalent to those of the olefin itself. The two planes containing respectively the bromonium ring and only the Br^+ are true symmetry planes. The third plane, containing only the two carbons of the bromonium ring, can be an "effective" symmetry element

arising from fast chemical exchange of Br^+ between the two sides of the plane itself. The protons at the opposite side of this plane are syn and anti to Br^+ and, in the low exchange limit, at lower temperature, have different chemical shift and the last effective plane of symmetry is lost, as shown in the lower part of the figure.



Scheme 8.

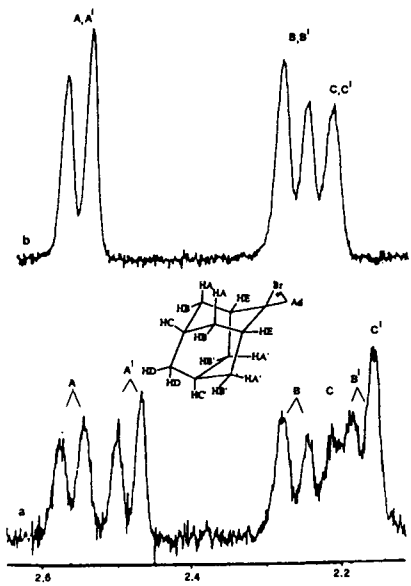


Fig. 6. ^1H NMR spectra of d_4-DCE solutions of adamantylideneadamantane (2 x 10^{-3} M) and Br_2 (7.5 x 10^{-1} M) at - 10°C (a) and + 38°C (b).

The k_{NMR} have been calculated by line shape analysis using the DNMR3 computer program. They were slowed down both by decreasing the temperature and by increasing the Br_2 concentration, and were found to fit equation (6), with y = -2.6. This is consistent with an exchange mechanism in which k_{NMR} is given by equation (7), where K_1 to K_4 are the equilibrium constants for the formation of 1:1 to 1:4 olefin-Br_2 aggregates. Under the employed experimental conditions equation (7) can be simplified to the equation (8). These equations imply that the rate determining step for the exchange mechanism is the interconversion of a 1:1 olefin-Br_2 complex. Figure 7 reports the energy profile for the exchange process. The figure visualizes why the exchange rate decreases so markedly with increasing Br_2 concentration. Such increase converts more of the total complex in solution into the lower energy Br_5^- and Br_7^- components, thereby decreasing the amount of 1:1 complex from which the exchange occurs.

$$k_{NMR} = A \cdot T \cdot e^{-(X/RT)} \cdot [Br_2]^y \qquad (6)$$

$$k_{NMR} = \frac{k_0 K_1 / K_3}{K_1 / K_3 + K_2 / K_3[Br_2] + [Br_2]^2 + K_4 / K_3[Br_2]^3} \qquad (7)$$

$$k_{NMR} = \frac{k_0 K_1 / K_3}{[Br_2]^2 + K_4 / K_3[Br_2]^3} \qquad (8)$$

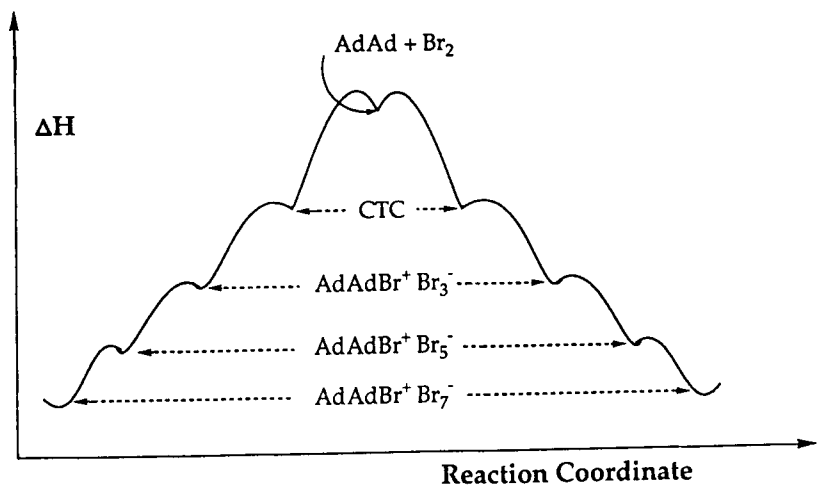
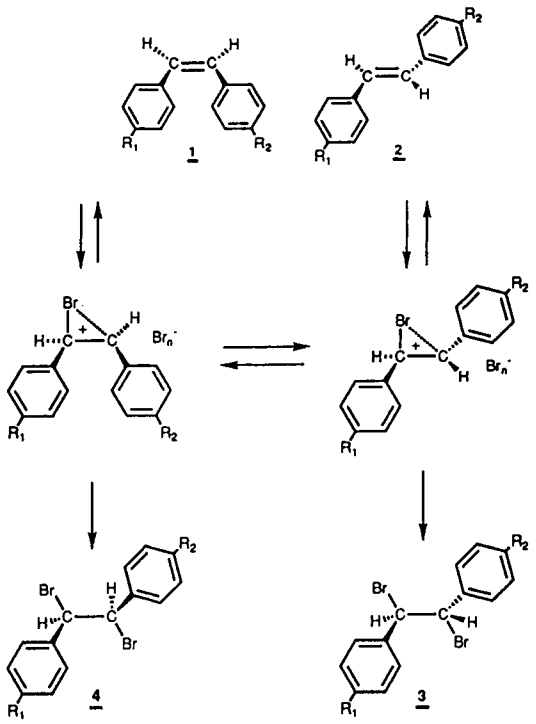


Fig. 7. Energy profile for the interconversion of complexes of adamantylideneadamantane with Br_2

Most of the olefins shown so far, for which reversibility of the bromonium ion formation had been demonstrated, are particular olefins, in which either steric bulk impedes the product forming step, or ring strain in the dibromide product retards this step. In order to check the general occurrence of the reversibility during the bromination reaction, a further approach, based on the cis-trans isomerization of stilbene derivatives during the bromination of the cis isomers, was devised.

If return occurs during the bromination of *cis*-stilbenes and rotation around the C-C bond is faster than collapse of the intermediates to dibromides, this process will lead to *trans*-stilbene (Scheme 9). We used this test to check the possibility of return in the bromination of unsubstituted, 4-methyl, 4-trifluoromethyl-, and 4,4'-bis(trifluoromethyl)-stilbenes in DCE (ref. 24). All these olefins gave clean third-order rate constants spanning 7 powers of 10. For each cis-trans couple the cis olefin was brominated 3.5 to 5.5 times faster than the trans isomer. Reactions for products analysis were performed at initial molar ratios of Br_2 to olefin of 1 to 2, so that products arose only from the cis olefin, the trans isomer being accumulated in the reaction medium.



Scheme 9. Bromination of cis and trans stilbenes

The product distributions obtained from the cis and trans isomers are reported in Table 7.

Table 7 : Product Distribution in the Bromination of Stilbenes in 1,2-Dichloroethane at 25°C. [a]

Olefin	*p*-CH_3		*p*-H		*p*-CF_3		*p,p'*-CF_3	
M	**2**:(**3**+**4**)	**3** : **4**	**2**:(**3**+**4**)	**3** : **4**	**2**:(**3**+**4**)	**3** : **4**	**2**:(**3**+**4**)	**3** : **4**
1								
2×10^{-1}	0.025	68 : 32	0.070	52 : 48	0.10	72 : 28		
1×10^{-1}							0.25	45 : 55
2×10^{-2}	0.055	68 : 32	0.10	53 : 47	0.15	73 : 27	1.20	64 : 36
1×10^{-2}							1.60	82 : 18
5×10^{-3}							2.10	> 95 : 5
2×10^{-3}	0.060	68 : 32	0.17	55 : 45	0.30	76 : 24		
2×10^{-4}	0.070	68 : 32	1.20	82 : 18	1.25	95 : 5		
2								
2×10^{-1}		70 : 30		68 : 32		82 : 18		> 98 : 2
2×10^{-3}		70 : 30		72 : 28		85 : 15		> 98 : 2
2×10^{-4}		71 : 29		84 : 16		95 : 5		> 98 : 2

[a] From ref. 24.

With the 4-methyl derivative both dibromides were stereoconvergently formed in a 7:3 ratio, indicating the intervention of an open ion intermediate, and the ratio of the trans olefin to the dibromides was very low. For the other derivatives a stereoconvergent and a stereoselective formation of the meso (or erythro) dibromide was observed only at sufficiently low reagents concentrations and the ratio of the trans olefin to the dibromides increased with increasing dilution. This behaviour points to an equilibration of the intermediates formed from either isomer of the cis-trans couple to a bridged trans ion which can either collapse to the meso (or erythro) dibromide or revert back to the trans olefin. Any acid-catalyzed or free radical-catalyzed cis-trans isomerization was excluded. So the **2**/(**3**+**4**) ratios obtained at the lowest concentration for the unsubstituted, trifluoromethyl substituted and bis(trifluoromethyl) substituted stilbenes give a measure of the relative rates of return of the trans ions to the trans olefins and of their collapse to dibromides. The results show that return is unimportant for the methyl derivative, where the intermediate is an open β-bromocarbonium ion, but is important for the other olefins, especially the bis(trifluoromethyl) derivative, where the intermediate is a bridged ion. This is reasonable, since the barrier for the product forming step would be expected to be higher in the case of a bridged ion, where nucleophilic attack by the counteranion at carbon requires a simultaneous breaking of one of the

bromonium C-Br bonds, than for an open bromocarbonium ion involving an easier collapse of the anion at the carbonium ion centre.

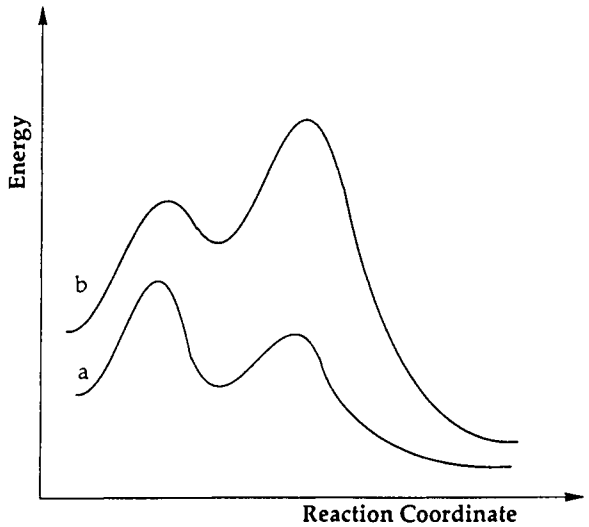


Fig. 8. Reaction coordinate diagram for the bromination of *trans*-4-methylstilbene (a) and *trans*-4,4'-bis(trifluoromethyl)stilbene (b).

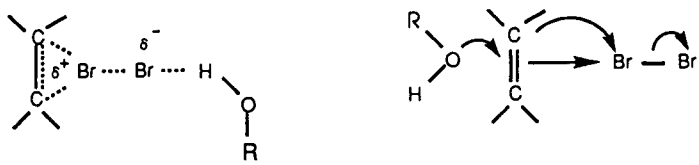
Reaction coordinate diagrams for the two extreme cases should be of the type shown in Figure 8 : the formation of a β-bromocarbonium ion intermediate from 4-methyl-stilbene is completely rate determining, while both the formation of the trans bromonium ion and the following dibromide formation are partially rate determining in the case of 4,4'-bis(trifluoromethyl)stilbene. So, a part of the very large difference in k_3 found for the bromination of these two olefins appears to be due to the high extent of reversibility and to partial rate determination during the product forming step of the latter.

Reversible formation of ionic intermediates in halogenated solvents has been suggested to be due to the weakly nucleophilic character of the counteranion, the tribromide ion, which should dissociate into nucleophilic bromide and free bromine before reacting with the bromonium ion (refs. 11,25,26). In order to check this hypothesis the product distribution of the *cis*-stilbene bromination in chloroform was investigated (ref. 27). In the latter solvent the formation constant of Br_3^- is considerably lower than in DCE, $K_f = 2.77\ (0.13) \times 10^4\ M^{-1}$ against $> 2 \times 10^7\ M^{-1}$. (ref. 28). As a consequence, at 10^{-3} M $[Br_2]$ relevant amounts of bromide ions are present as counteranion of the bromonium intermediate. Nevertheless, the same trend for the isomerization of *cis*- to *trans*-stilbene, as well as an increase of

stereoselective formation of the meso-dibromide with decreasing reagent concentrations, was found also in chloroform (ref. 27).

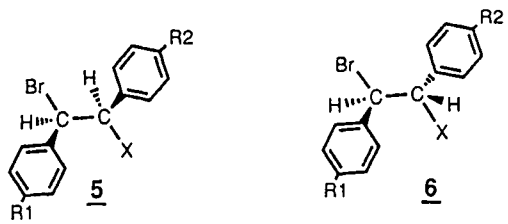
The occurrence of the same cis-trans isomerization observed in chlorinated hydrocarbons was finally tested for substituted *cis*-stilbenes in two protic solvents, acetic acid and methanol, where the counteranion is a Br^- instead of a Br_3^-.

In these solvents at sufficiently low Br_2 concentration ($< 10^{-3}$ M) the kinetics are first order both in the olefin and in Br_2 and the main solvent effect consists of an electrophilic solvation of the departing Br^- ion. A nucleophilic assistance by hydroxylic solvents has also been recognized recently (ref. 26) (Scheme 10). So far, return during the olefin bromination in methanol had been admitted only for alkylideneadamantanes, and was ascribed to steric inhibition to nucleophilic attack at carbons of the bromonium ion (ref. 26).



Scheme 10.

The investigated *cis*-stilbene derivatives, 4-methoxy, 4,4'-dimethyl, unsubstituted, and 4,4'-bis(trifluoromethyl)stilbenes, had k_2 values spanning 6-7 powers of ten both in methanol and in acetic acid. Products **3**, **4**, **5** and **6** were formed. Table 8 reports the results of the cis-trans isomerization test in acetic acid (ref. 29). No acid catalyzed or free radical process was found to be responsible for these isomerizations.



X = OCH_3, or OAc

Table 8 : Brominations of Stilbenes in Acetic Acid at 5 x 10^{-2} M Bromine and 10^{-1} M Olefin at 25°C

1	2 / Total Products		2 / (3 + 6)	
		a		a
$R_1 = R_2 = H$	0.4	0.025	1.5	0.06
$R_1 = R_2 = CH_3$	0.007	0		
$R_1 = H$ $R_2 = OCH_3$	0.007	0		
$R_1 = R_2 = CF_3$	0.62	0.08	6.2	0.5

[a] Reactions carried out in the presence of 0.5 M $LiClO_4$

Table 8 shows the ratios of the trans olefin to the bromination products obtained in reactions carried out in acetic acid in the absence and in the presence of 0.5 M $LiClO_4$. Like in DCE, no isomerization was observed for stilbenes bearing electrondonating substituents able to stabilize bromocarbonium ions, while extensive isomerization occurred with stilbene itself and even more with its bis-(trifluoromethyl) derivative. In the latter case the intermediates are surely strongly bridged bromonium ions and the ratio between return of the trans bromonium ion and its collapse to dibromide and solvent incorporated product (3+6) is around 6, showing an high barrier for nucleophilic attack at the bromonium carbons. However, return was practically suppressed by the presence of $LiClO_4$. The perchlorate anion exchanges with bromide in the ion pairs and prevents return and collapse to dibromide in favour of solvent incorporation.

Similar results were obtained in methanol (ref. 30), where for the bis-(trifluoromethyl) derivative the ratio between the return of the trans bromonium ion to the trans olefin and its collapse to products 3 and 6 is 4.5 and is again very strongly reduced by the presence of $LiClO_4$ (Table 9). In this solvent, however, return was not observed for unsubstituted stilbene, either. It can be observed that both *cis* - and *trans* -stilbene gave methoxybromo adducts in an anti stereospecific way, suggesting a nucleophilic assistance by the solvent.

Table 9 : Brominations of Stilbenes in Methanol at 5 x 10^{-3} M Bromine and 10^{-2} M Olefin at 25°C

1	2 / Total Products		2 / (3+6)	
		a		a
$R_1 = R_2 = H$	0			
$R_1 = R_2 = CH_3$	0			
$R_1 = H$ $R_2 = OCH_3$	0			
$R_1 = R_2 = CF_3$	0.41	0.12	4.5	0.9

[a] Reactions carried out in the presence of 0.5 M $LiClO_4$

CONCLUSIONS

The present results show that the first step of the interaction between olefins and Br_2 is the formation of CTCs, whose K_f are highly sensitive to structural effects. Both K_f ratios and reactivity ratios of olefins are scarcely affected by the solvent. An increase by two in number of alkyl substituents on the double bond increases both K_f and k_{obsd} roughly by a factor of 10^3. Therefore, at variance with the expectation for an Ad_EC1 mechanism, substituent effects are not much more influential on k_{obsd} than on K_f. This suggests that the rates of CTC ionization be actually reduced by reversal.

This reversal has been demonstrated by both product and kinetic studies. In the absence of solvent nucleophilic assistance and of substituents favouring β-bromocarbonium ion intermediates, the ionization of CTC's to bromonium (poly)bromide has been shown to occur not only for congested olefins, but more generally for "normal" olefins both in aprotic chlorinated hydrocarbons and in protic solvents like acetic acid and methanol.

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SYNTHESIS OF A METABOLITE OF FANTOFARONE

GILBERT ROSSEELS, CHRISTIAN HOUBEN, PATRICIA KERCKX

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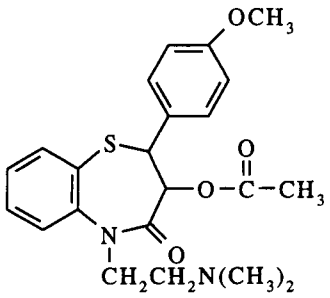
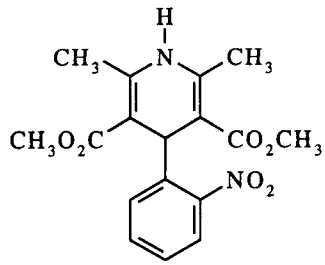
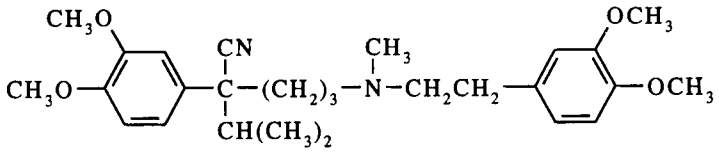
Despite the growth in interest in calcium blockers, there are comparatively few calcium channel blocking agents currently in clinical use. These drugs are characterised by the fact that they belong to classes of compounds which are chemically unrelated like Diltiazem®, Nifedipine®, Verapamil®, Fluspirilene® and some others (Scheme 1).



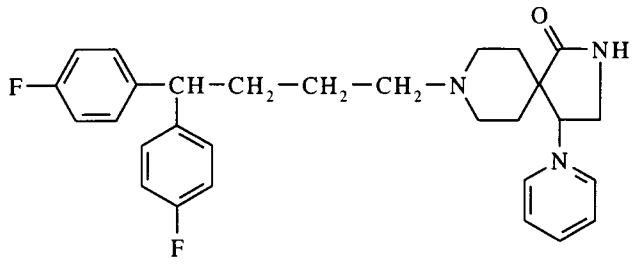
Diltiazem®



Nifedipine®



Verapamil®



Fluspirilene®

Scheme 1. Calcium channel blocking agents.

What diseases are calcium blockers useful for ?

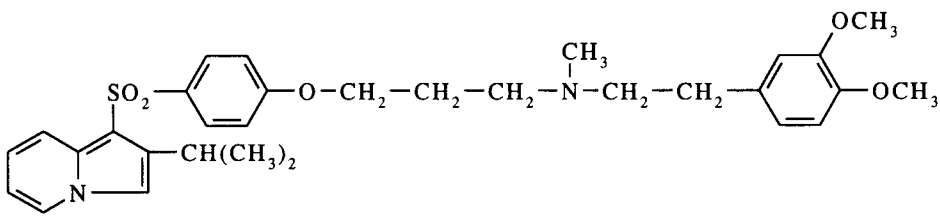
They are useful against hypertension but also for cases of angina, heart failure, heart attack, arythmia, silent ischemia, stroke and senility.

Silent ischemia is atherosclerosis that has begun to affect the heart adversely but does not yet show symptoms.

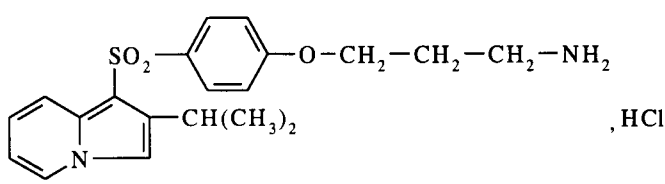
How does a calcium blocker work ?

One source of calcium ions, which cause contraction of smooth muscle in arterial walls, is inflow through ion-specific channels. So, the calcium blockers block the channels, limiting inflow of calcium and keeping muscle cells in relaxed states for a longer time.

Previous studies by us have led to the discovery of 1-sulfonylindolizines as a new class of potent calcium antagonists (refs 1,3,4 ; Scheme 2).



SR 33557



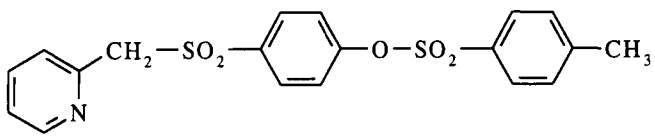
SR 34366A

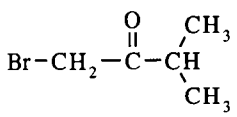
Scheme 2. New class of potent calcium antagonists.

One of the compounds in this group, SR 33557 (DCI: fantofarone), has been selected for clinical development.

We will describe later in this article the synthesis of one of the metabolites of fantofarone, SR 34366A, previously prepared by S.N. Kilenyi and J. Mahaux (ref. 5) in these laboratories.

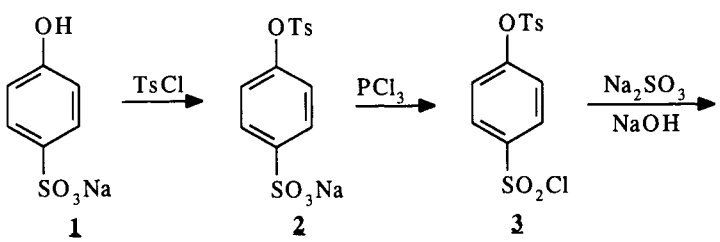
The SR 33557 was prepared starting with two building blocks : a picolylsulfone and an α-bromomethylisopropyl ketone (Scheme 3).

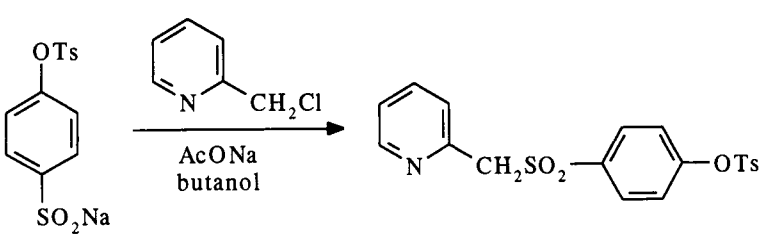




Scheme 3. Starting materials of SR 33557.

The picolylsulfone **5** is obtained by a reaction involving the conversion of a sulfonate sodium salt **2** into a sulfinate sodium salt **4** and reaction of the latter with 2-picolyl chloride (refs 6,7 ; eqn. 1).

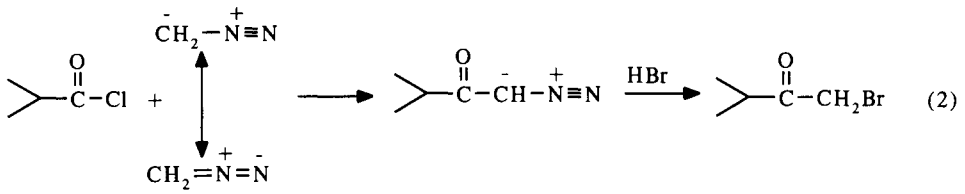




(1)

4 **5**

At the laboratory scale, the α-bromoketone was prepared by an Arndt-Eistert reaction which gives the good isomer in a univocal way (eqn. 2).

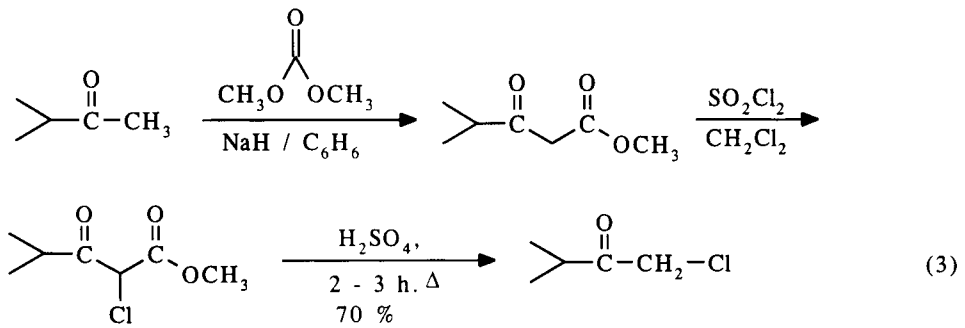


(2)

The reaction needs diazomethane and this reagent is too dangerous for industrial use.

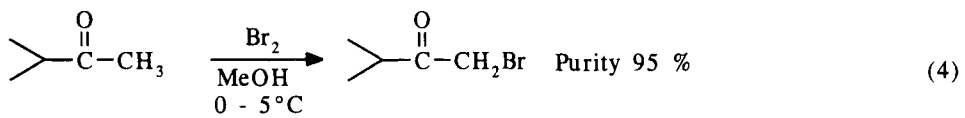
Furthermore we applied also the procedure of De Kimpe et al. (ref. 8).

The first step is the preparation of the β-ketoester easily accessible by condensation of methylisopropylketone with dimethylcarbonate in benzene in the presence of sodium hydride. Chlorination of this β-ketoester with sulfuryl chloride in dichloromethane occurred smoothly at room temperature affording the methyl 2-chloro-3-oxoalkanoate free from side products. The acidic splitting of the latter with 50 % sulfuric acid under reflux gives a yield of 70 % pure product, free from the isomeric form (eqn. 3).



(3)

Actually, at industrial scale, we use a direct bromination method with bromine in methanol at low temperature (eqn. 4).

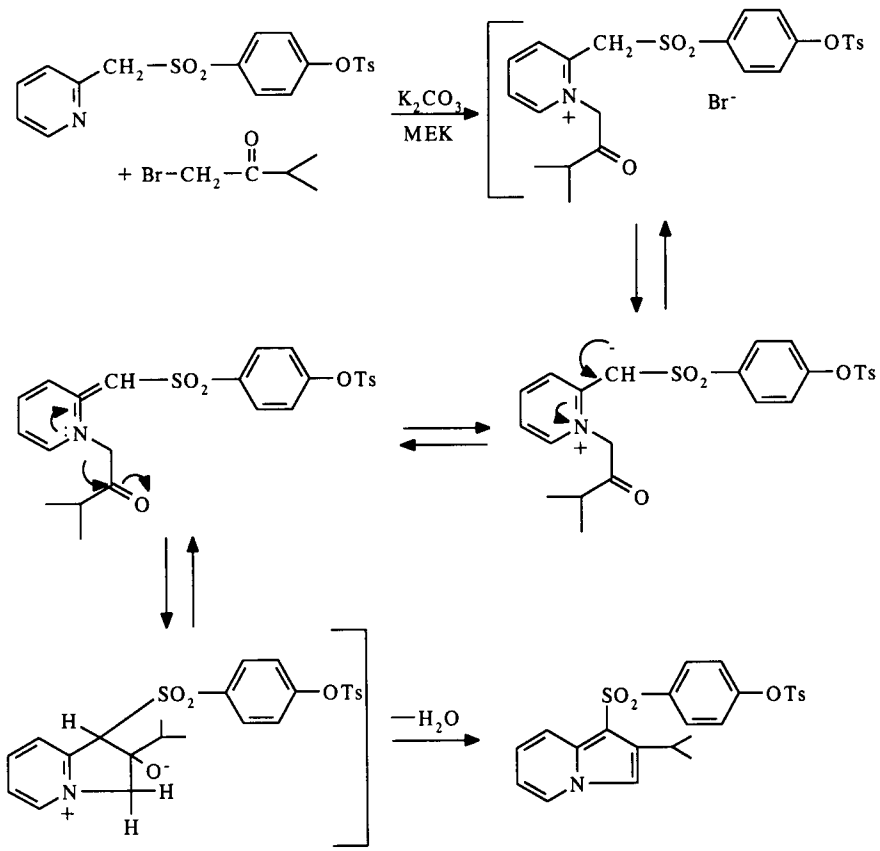


(4)

The procedure of Gaudry & Marquet (ref. 9), in contrast to other methods, comprises only one step and is readily adapted to large scale preparative work. Furthermore, dibromination is very slow in methanol and hence the crude reaction products contain only traces of dibromoketones when using methanol. Methanol is then recommended as a brominating solvent even when no orientation problem is involved.

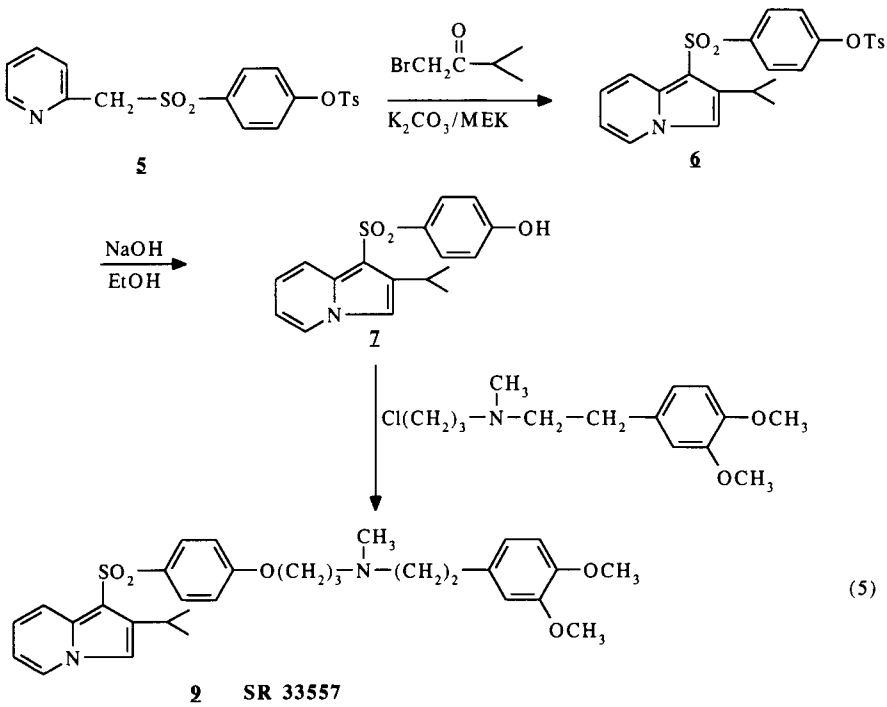
With the two starting compounds, the picolylsulfone and the α-bromoketone we applied the well known Tschitschibabin synthesis (ref. 10). The first step of this synthesis is the formation of a quaternary pyridinium salt.

Although the exact mechanism of the Tschitschibabin cyclisation has not been elucidated, it is reasonable, as shown in Scheme 4, to assume a series of reversible steps from the vinylogous ylide (or methylide) to a methine and an enol-betaine intermediate and then finally an irreversible dehydration to the indolizine nucleus. The reaction might be related to the modern electrocyclic 1,5 dipolar cyclization.



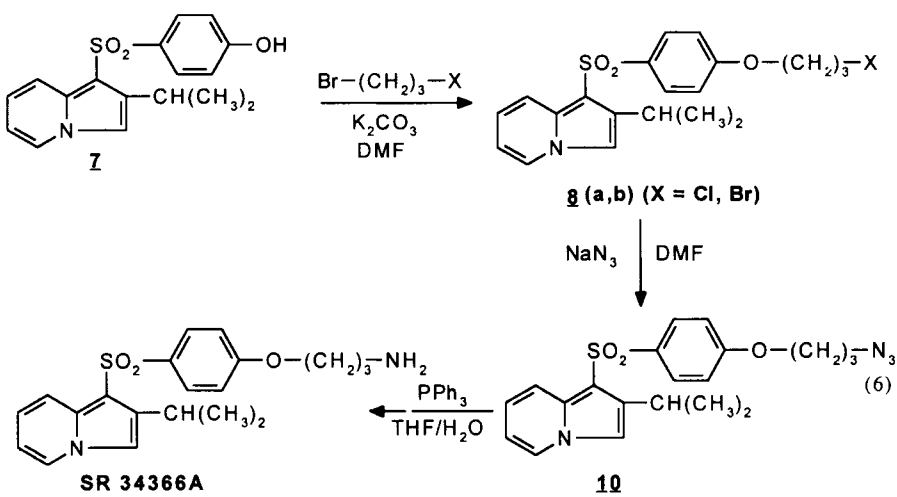
Scheme 4. Mechanism of the Tschitschibabin cyclisation.

This tosylester is hydrolised with sodium hydroxide in ethanol to give the corresponding phenol 7 (eqn. 5).



(5)

The SR 33557 is obtained by alkylation of phenol 7 with the appropriate chloroalkylamine.



(6)

The reaction of 1-halo 3-bromo propane with the phenol gives the halo-propoxy derivatives **8a** (X=Cl) and **8b** (X=Br). The reaction proceeds in DMF, MEK or toluene at reflux in the presence of potassium carbonate but also at room temperature in DMSO (eqn. 6).

In both cases we could not exceed a HPLC purity of about 84-85 %. The same symptom appears in other heterocyclic series and is due to the fact that there is always formation of the allyloxy derivative and in some cases formation of the disubstituted compound.

Sometimes it is possible to separate them by preparative chromatography but these two side products do not interfere in the following reaction.

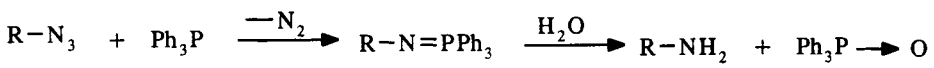
The two halopropoxy compounds react with sodium azide in DMF to afford the azido intermediate **10**. We used the method of KNOUZI et al.(ref. 11) but we replaced DMSO by DMF.

With the chloropropoxy derivative **8a** the reaction mixture was boiled at 60°C for 18 h. and gave a yield of only 16 % pure product.

However, with the bromopropoxy derivative **8b**, the reaction proceeded at 20°C for 12 h. with a yield ranging from 84 to 100 %.

The azido compound **10** reacts with 1.5 equiv. of triphenylphosphine in DMF in the presence of THF and 1.5 equiv. of water to give the final product, SR 34366A with a quantitative yield.

The proposed reaction mechanism (Scheme 5) is :



Scheme 5. Proposed mechanism for reaction of triphenylphosphine with the azido compound.

It is interesting to note the chemoselectivity of the reaction : double and triple bonds, thioketals, epoxides, nitro and sulfone groups and usual functions are not affected.

PHARMACOLOGY

Pharmacological experiments were carried out (refs. 1,3,4).

Binding Assay

IC_{50} was determined as the drug concentration which inhibited 50 % of the specific binding of the ligand.

The IC_{50} values for the inhibition of [^{3}H]-nitrendipine binding for the metabolite has a value of 203 nM in comparison to SR 33557 which reaches a value of only 0.6 nM.

The vasorelaxant activity, which was assessed as the inhibition of calcium-induced contraction of K-depolarised rat aorta has a IC_{50} of 3368 nM compared with 5.6 nM for SR 33557.

Hemodynamics

No α, β_1 and β_2 activity at 0.1 mg/kg (anaesthetized dog).

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2-BROMOAMIDES. STEREOCONTROLLED SUBSTITUTION AND APPLICATION TO THE SYNTHESIS OF COMPOUNDS OF BIOLOGICAL INTEREST

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SUMMARY

2-Bromoamides are interesting and versatile intermediates for substitution of bromine by a variety of nucleophiles and for other synthetic approaches. Whereas emphasis is given to chiral 2-bromoamides, congeners carrying a tertiary or primary C-Br function have also been investigated.

Among the peculiar features of 2-bromoamides there are the following : i) possibility of substitution at the tertiary C-Br (RCO_2H, RR'NH, or a saccharide, as the nucleophiles); ii) chiral stability and stereochemical control at the secondary C-Br atom (RR'NH, ROH or a saccharide as the nucleophiles); iii) the presence of bromine allows cyclic voltammetry and electroreduction at controlled potential both of starting compounds and relevant intermediates; iv) the Cα polarity can be reversed upon electroreduction, and the resulting Cα enolate forms a C-C bond (CO_2 as the electrophile).

Application of the bromine substitution reaction allows the synthesis of aminoamides, alkoxyamides of simple alcohols and sugars, depsipeptides and Ψ (NH) pseudopeptides, C_2 symmetric compounds.

INTRODUCTION

In spite of the fact that biotechnology rather than chemical processing will probably provide the future greatly needed chirally pure compounds (ref. 1), we believe that simple chemical reactions starting from chiral natural compounds and proceeding under stereochemical control will eventually retain full importance. On the above grounds, we report on simple reactions which start from α-aminoacids, as an example of utilization of natural compounds, and move to related bromine containing compounds (Fig. 1).

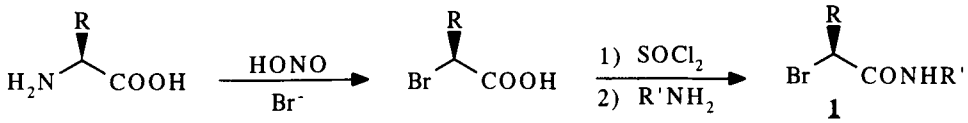


Fig.1.

It is well known that diazotization-bromination of a natural aminoacid, yields the corresponding (S)-2-bromoacid with retention of configuration (ref. 2). The bromoacid is easily transformed into the corresponding (S)-2-bromoacyl chloride and finally, (S)-2-bromoamide. The resulting NH protic (S)-2-bromoamides **1** offer the peculiar combination of the bromide leaving group and the adjacent amide hydrogen. Compared to 2-acyloxyesters as the tosylates (ref. 3) and nosylates (ref. 4) which can also be obtained from natural aminoacids via hydroxyacids, 2-bromoamides **1** undergo direct nucleophilic substitution with inversion of configuration, as do the 2-acyloxyesters : however, a faster, competitive nucleophilic substitution with retention of configuration, stems as a consequence of their ambifunctional features (ref. 5). While a variety of 2-aminoamides **2** and a representative quaternary ammonium derivative **3** are regio-and stereo-selectively obtained upon reactions of chiral 2-bromoamides **1** with amines (ref. 5), N-mesyloxyamides react with amines to give either the expected or the rearranged (Favorskii-like) aminoamide (ref. 6), as earlier found with 2-haloamides in the presence of strong bases.

The present stereoselective syntheses using chiral 2-bromoamides involve a reappraisal of the role of bromine as a leaving group, and of silver containing promoters, in particular silver oxide (Ag_2O). Whereas "moist Ag_2O" is a long known ingredient of halogen/hydroxyl substitution, in the present circumstances, Ag_2O behaves as a sofisticated coupling agent, capable of activating the 2-bromoamide molecule. Regioselective substitution of bromine by an available nucleophile, according to its nucleophilic power, follows.

RESULTS

In recent studies, we found that primary and secondary amines, alone or somehow faster in the presence of the soft Lewis acid Ag^+ (refs. 7-9) substitute the bromine in (S)-2-bromopropanamides, in an organic solvent, at room temperature, and yield N-alkyl-, and N,N'-dialkyl-aminopropanamides, with inversion of configuration and high enantiomeric excess. Conversely, in the presence of silver oxide (Ag_2O), much faster reactions occur with retention of configuration, giving

the enantiomeric N-substituted 2-aminoamides, also with high yields and e.e.s. (ref. 5).

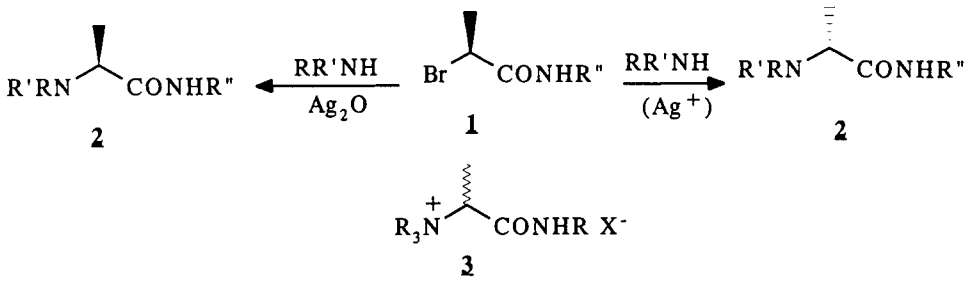


Fig. 2.

A number of (S)- or (R)-2-aminoamides were independently obtained by running reactions between chiral 2-bromoamides **1** and an achiral primary or secondary amine, in both sets of conditions (ref. 5). Accordingly, either a diastereoisomeric mixture or a single diastereoisomer in high diastereoisomeric excess, resulted respectively when an (S,R)- or (S)-2-bromoamide is treated with a chiral amine, again in the two sets of conditions.

An alcohol is an example of a compound which does not react with a 2-bromoamide, in the absence of a promoter. Representative reactions (Fig. 3), with methanol in the presence of Ag_2O, gave an (S)-O-methyllactamide **4** rapidly and with retention of configuration. To explore if an alternative stereochemistry was available and to have indirect information on the role of Ag_2O, reactions were also run between methanol and a 2-bromoamide, in the presence of $Ag^+CF_3SO_3^-$. The inversion product (R)-O-methyllactamide was obtained rapidly, with high yield (ref. 10).

Substitution reactions where the nucleophilic group was a single free hydroxyl group of a saccharide, the other ones being protected, were also studied. The expected ether-amides or glycoside-amides were obtained from 2-bromoisobutyramides (ref. 11) and/or from chiral or racemic 2-bromopropanamides, in the presence of Ag_2O (ref. 12). Compound **5** is a partially protected ether-amide resulting from an (S)-2-bromo-propanamide and a saccharide with a free hydroxyl at C-6 (Fig. 3).

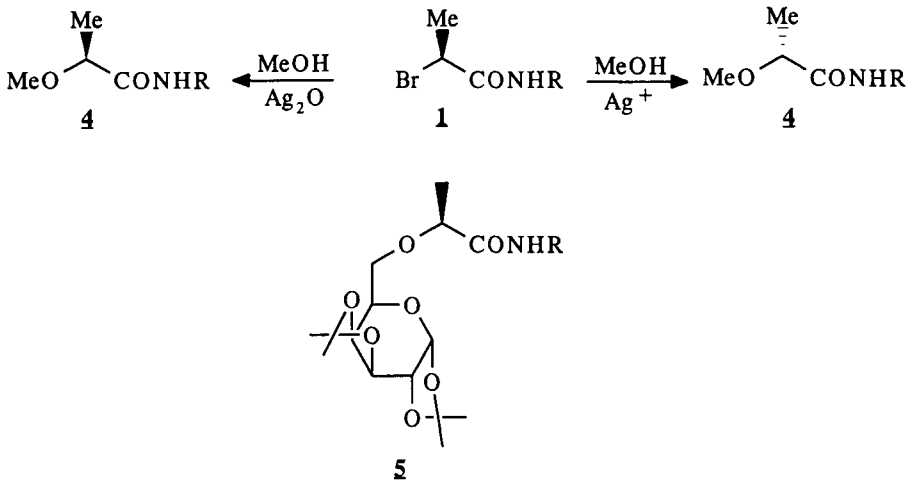


Fig. 3.

ON THE CHIRAL STABILITY OF 2-BROMOAMIDES AND RELATED COMPOUNDS

E. Gil-Av and associates (ref. 13) proved that 2-bromoamides represent suitable derivatization products allowing to check, via chiral columns, the optical purity of 2-bromoacids arising from α-aminoacids upon diazotization. The results are relevant, since i) 2-bromoacids, as well as some related derivatives, had been considered chirally unstable, and ii) by increasing the concentration of HBr in the diazotization of an aminoacid, the ratio bromoacid vs hydroxyacid increases, but the optical yield decreases, due probably to S_N2 reaction by bromide anion.When we allowed to react a chiral 2-bromoamide with a variety of amines, in different molar amounts, we found that two enantiomeric or diastereoisomeric products arise competitively according to the different reaction conditions and intervening mechanisms (Fig. 2), and that a fully optically active substrate is recovered whenever the reaction is not allowed to reach its end. We can conclude that the fate of a chiral NH-protic 2-bromoamide, in the presence of a nucleophile and of coreagents employed in the investigation, is overwelmingly linked to nucleophilic substitution rather than to "racemization". Stereoselectivity obviously depends upon a favorable ratio between the rates of two competitive mechanisms that can operate (see below). By using an insufficient amount of Ag_20, infact, the optical activity of the produced aminoamide does decrease, because the rates of promoted and unpromoted reactions approach to each other (ref. 10).

As far as "racemization" is concerned, we checked further the optical stability of representative 2-bromoamides. Whereas (S)-2-bromopropananilide or the aprotic (S)-2-bromo-N-methylpropananilide are stable in ethanol or ethanolic triethylamine, slow racemisation was observed, at room temperature, for the latter compound (oil) and for both ones in ethanolic HCl (1-5 mol.).

MECHANISMS OF THE SUBSTITUTION REACTIONS

Both in the 2-bromopropanamides and some reaction intermediates, the presence of bromine allowed to use electrochemistry as a prominent tool for mechanistic studies and for syntheses by reduction at controlled potential.

Kinetic analysis showed that a good nucleophile, i.e. a primary or secondary amine, substitutes the bromine atom with inversion of configuration, through an S_N2 mechanism on the neutral 2-bromoamide (ref. 14). To open the way to understanding the mechanism of the heterogeneous reactions promoted by Ag_2O, kinetic analysis was performed in homogeneous conditions through electrochemical reduction of a parent 2-bromoamide (Fig. 4). The resulting electrogenerated base, enolate-amide **6**, produces, through proton transfer from **1**, the bromoamidate anion **7**. Electrochemical analysis of this intermediate, which undergoes electroreduction to dianion **8**, demonstrated that **7** decays before reacting with any available partner (ref. 14).

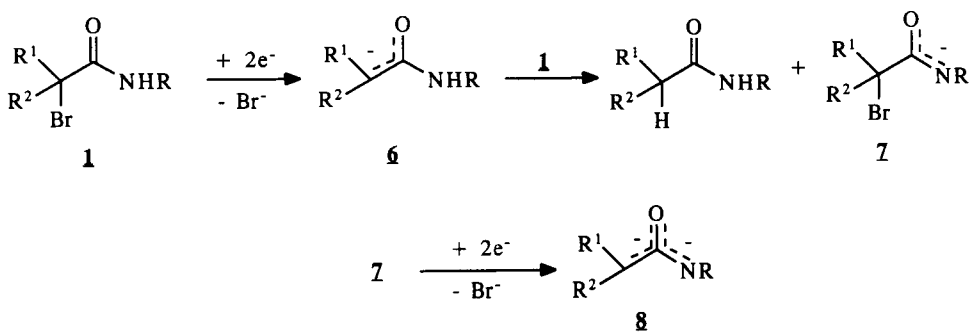


Fig. 4

The kinetics and stereochemical data definitely point to a transient aziridinone of inverted configuration **9** among the further potential intermediates (Fig. 5). Reactions of aziridinone **9** with a nucleophile would allow the crucial bond of the product **10** to form through a second inversion (overall retention). This pathway

was recently proposed to take also place in few reactions starting from a stable aziridinone (ref. 15).

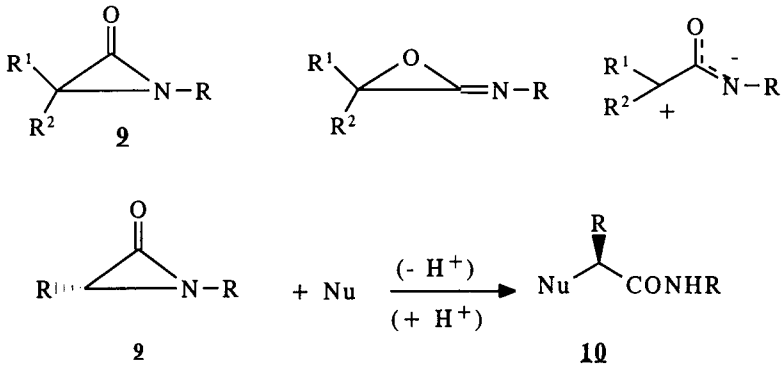


Fig. 5.

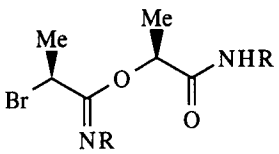
A good nucleophile, as is the case for most primary or secondary amines, can react through the two above mechanisms, either in the absence or presence of Ag_2O, affording the pertinent stereoisomeric substitution derivative. From a practical point of view, the presence of Ag_2O represents the best choice, since it grants faster reactions and full retention of configuration.

Polarity reversal and further alkylation studies

The electrochemical results suggested to explore the possibility of creating a C-C bond between the electrogenerated α-carbanion **6** and carbon nucleophiles. Results of practical importance have hitherto been obtained upon electroreduction of 2-bromoisobutyramides in acetonitrile at Hg or Pt cathodes, in the presence of carbon dioxide and an alkylating agent. The enolate-amide **6** undergoes quantitative carboxy-alkylation, to yield ester amides of 2,2-dimethylmalonic acid (ref. 16).

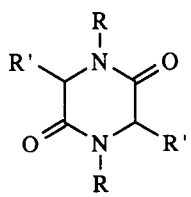
We also investigated the behaviour of 2-bromoamides in the presence of Ag_2O or Ag^+, but in adverse conditions provided by poor nucleophiles or no nucleophile added, etc. In the presence of Ag^+, bromine substitution by a hindered amine still takes place, albeit slowly or in low yield. Comparison with other samples, allow us to assign to the resulting products a retained configuration. We believe that the combination Ag^+/hindered amine induces the amine to behave both as a base and a nucleophile, grace to a shift from a mechanism of electrophilic assistance to an alternative one, where Ag^+ is responsible of an acidity-enhancement mechanism (ref. 10). Accordingly, the neighbouring-group pathway takes over, as is the case for reactions promoted by Ag_2O with common amines.

Water, which can be taken to a minimum by the use of molecular sieves, can produce a lactamide either through direct reaction with the aziridinone intermediate, or upon hydrolysis of oxazolidinone self-condensation products, previously obtained also in the presence of a strong non-nucleophilic base (H^-) (ref. 17). The recently reported O-self-alkylation compound **11** bears the (S,S)-configurations at the unreacted C-Br and newly formed C-O bonds. The presence of bromine was expedient for the x-ray assessment of configuration at the two chiral centers of **11** which forms in high diastereoisomeric excess (ref. 5).

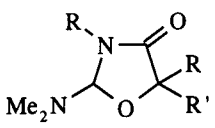


11

The intriguing formation of a few dioxopiperazines **12** opens new problems of competitive regiochemistry and stereochemistry. Related synthetic, x-ray, and theoretical studies are currently carried out (Ref. 18).



12



13

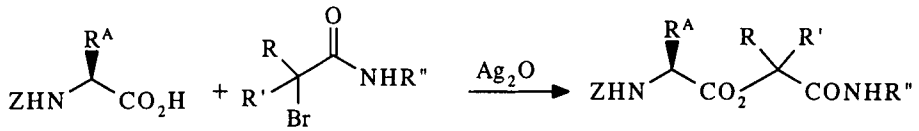
We previously described the cyclocoupling of 2-bromoamides onto the carbonyl group of a variety of amides, including 2-bromoamides themselves (ref. 17). The cyclocoupling with DMF affords 2-dimethylamino-oxazolidinone derivatives **13** (ref. 19). Its mechanism has been recently investigated (refs. 14,15b).

APPLICATION OF CHIRAL 2-BROMOAMIDES TO THE SYNTHESIS OF COMPOUNDS OF BIOLOGICAL INTEREST

Rationalization of the results obtained in the substitution reactions prompted their application to topics of current interest, such as studies on the structures and biological activities of peptides, depsi-peptides, pseudo-peptides, or C_2-symmetric

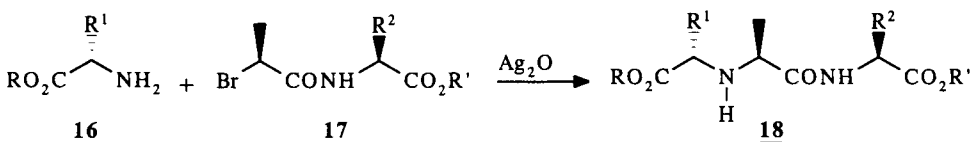
sequences. These applications are indicative of the great versatility of 2-bromoamides, and of the potential manyfold involvement of natural aminoacids. Each aminoacid may offer, infact, as the nucleophile, either its carboxyl group, or amino group, or the functional group of a side chain.

N-protected aminoacids **14** behave as carboxyl partners in Ag_2O promoted reactions of 2-bromo-isobutyramides or -propanamides affording, respectively, esters of 2-hydroxy-isobutyramides (ref. 20a) or lactamides **15** (ref. 20b). While we plan further research on stereochemical and other aspects of these reactions, model units obtained from 2-bromo-isobutyramides have been used in conformational studies of depsi-peptides (ref. 21).



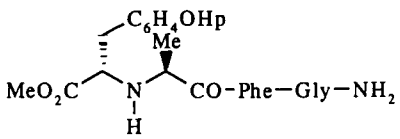
14 **15**

Esters of natural aminoacids **16** behave, in turn, as amino-partners towards an (S)-2-bromopropanoyl amino ester **17**. The (S,S)-2-bromopropanoyl aminoester **17**, resulting upon 2-bromopropanoylation of aminoester **16** is the simplest example of a diastereomeric 2-bromoamide which can behave as a building unit for ψ(NH) pseudopeptides or C_2 symmetric products. Reaction of **16** with **17** in the presence of Ag_2O affords the minimum entity incorporating an aminodicarboxyl unit **18**, with retention of configuration, and high yields (ref. 22a).



16 **17** **18**

Regioselective deprotection and/or alteration of the ester functions of the resulting aminoamide diester **18**, followed by elongation at the proper carboxyl or altered site through classic peptides synthesis, will afford a variety of partially artificial target peptides. Hitherto, few terminal ψ(NH) pseudopeptides (i.e. peptides having an NH group in place of a CONH group and a "reversed" carboxyl group) as **19** and **20**, related to the opioids peptides dermorphin and deltorphin-C have been obtained (ref. 22a). When tested for μ or δ receptor binding ability and in vitro behaviour, they provided interesting information (ref. 22b).



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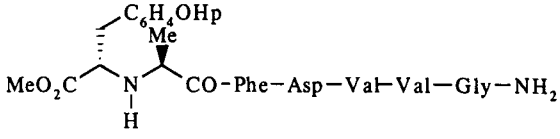
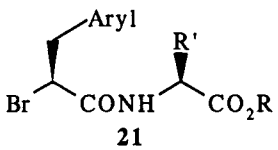


20

If a target aminodicarboxyl units bears an aryl group in one of its side chains, retrosynthetic analysis indicates that a bromoamide synthon 17, bearing an aliphatic side-chain, should react with a nucleophilic partner carrying the aromatic side chain. In the alternative bromoamide **21**, HBr elimination to cinnamic derivatives competes with the desired bromine substitution.



21

When the two partial sequences stemming from the central NH group are chemically and stereochemically identical, C_2 symmetric products result. We consider such compounds as candidates for biological studies, as well as models of C2 chiral auxiliaries for asymmetric induction (ref. 23), or ligands for metal ions. Syntheses of C_2 symmetric compounds requiring the use of chiral auxiliaries have been recently reported (ref. 24).

Many 2-bromoamides were tested for toxicity or mutagenicity : 2-bromo-N-benzyl-propanamide showed mutagenic effects, unrelated to its configuration (ref. 25).

CONCLUSIONS

2-Bromopropanamides and related chiral bromoamides enjoy full stereochemical stability, while undergoing stereoselective bromine substitution by a variety of nucleophiles (primary, secondary and tertiary amines, carboxylic acids, alcohols, saccharides, aminoacids, etc..). Whereas Ag_2O proved the best promoter of bromine substitution, due to high reaction rates and retention of configuration, Ag^+ (as CF_3SO_3Ag) was expedient to accelerate single reactions, either through electrophilic assistance or acidity-enhancement mechanisms. Novel altered peptide structures are obtained upon reaction of 2-bromoamides with aminoacids. The

composite role of bromine as a versatile functional group and of α-aminoacids as sources of chirality, stand on the following : i) diazotization-bromination of a natural aminoacid gives a 2-bromoacid with retention of configuration; ii) 2-bromoacylation of a (2nd) aminoacid affords a synthon **17** which iii) reacts at the C-Br bond with a (3rd) aminoacid acting as a nucleophile, according to the protection adopted, either with its carboxyl or amino group, or with the functional group of a side chain. iv) the resulting minimum entities of a depsipeptide, or (ψNH) pseudo-peptide, or C_2 symmetric compounds can be elongated by classic peptide synthesis and/or proper repetition of the enantioselective monoalkylating performance of 2-bromoamide synthons. v) a variety of structures and related structure-reactivity studies are programmed.

Electrochemical methods allowed to shed light on the different reaction mechanisms, both in homogeneous and heterogeneous (Ag_2O promoted) systems. Furthermore, electroreduction reverses the C-Br bond polarity, allowing the formation of a C-C bond with an electrophile (f.ex. CO_2).

ACKNOWLEDGMENTS

We are grateful to CNR and MURST for financial support and to Dr. F. Maran for a critical reading of the manuscript.

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ASYMMETRIC SYNTHESIS OF (S)-α-SUBSTITUTED β-BROMO-α-HYDROXY ACIDS

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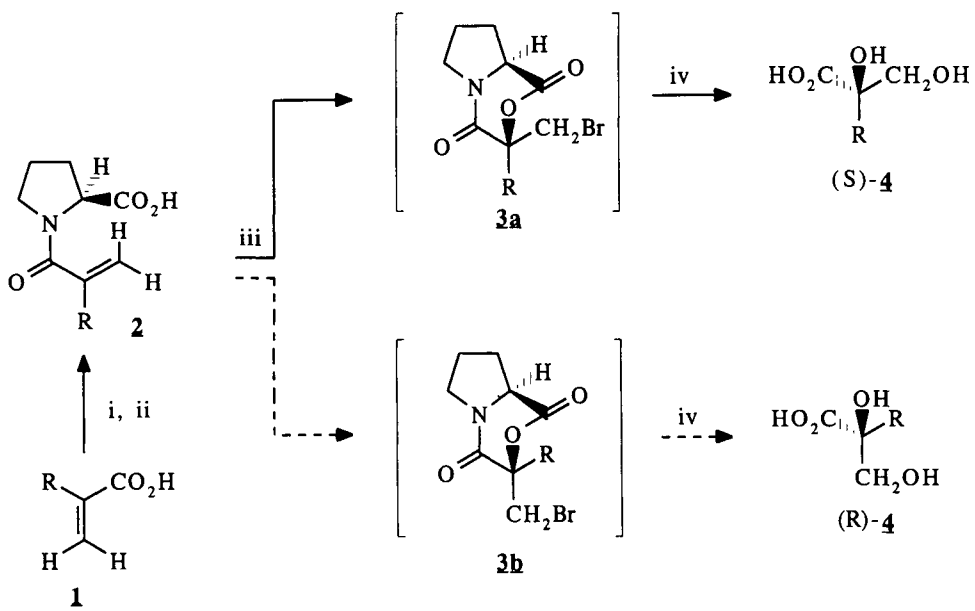
(S)-α-substituted β-bromo-α-hydroxy acids (S)-**4** are very important chiral synthon for medicinally important compounds, such as potential new hypoglycemia active alkylglycidic acids (ref. 1) and anti-ulcer active misoprost (ref. 2).

Herein we will show a new and simple synthetic method for (S)-**4** using asymmetric bromolactonization which has been the most dependable method for the chiral α-α-disubstituted α-hydroxy acids (ref. 3).



i) (S)-ethyl prolinate (1.0) - DEPC (1.1) - TEA (1.1) - DMF (0°C, 2 hrs then rt, 24 hrs)
ii) KOH (1.1) - H_2O - MeOH (1:1) (rt, 4 hrs). iii) NBS (2.0) - DMF (0°C, 2 hrs then rt, 24 hrs)
iv) 6N - HCl (reflux, 24 hrs)

Scheme 1. Asymmetric synthesis of (S)-α-substituted β-bromo-α-hydroxy acids

As shown in scheme 1, (S)-amide **2** (ref. 4) obtained from ethyl ester of (S)-proline, chiral auxiliary and 2-substituted-2-propenoic acids **1** are bromolactonized with N-bromosuccinimide (NBS)-DMF, followed by hydrolysis with 6N-HCl to afford (S)-**4**. The results are summarized in Table 1.

Table 1. Asymmetric synthesis of (R)-α-Substituted Glyceric Acids, (R)-**4**.

	R	(S)-**4**			
		$[\alpha]_D^{20}$, c)	Yield (%)	% ee	Config.
a	CH_3	- 8.04 (0.28) [a]	96	97 (ref. 6)	R (ref. 6)
b	C_2H_5	- 6.88 (0.80) [b]	75	88 (ref. 6)	R (ref. 6)
c	n-C_4H_9	- 5.82 (0.55) [b]	86	98 (ref. 6)	R (ref. 6)
d	$CH_2C_6H_5$	- 8.29 (0.35) [b]	95	96 (ref. 6)	R (ref. 6)

a), b) Optical rotations are observed in EtOH and $CHCl_3$, respectively.

As seen in Table 1, (S)-**4** are obtained in excellent chemical and optical yields by using the neutral and mild key reaction, the bromolactonization, followed by simple treatment with HCl.

In view of the absolute configuration and their optical yields (88-96 %), it follows that the precursor of the (S)-**4** should be **3a**, which are formed highly diastereoselectively. It is likely that the predominant formation of **3a** conforms to the mechanism of the bromolactonization, the S-trans transition state (ref. 3).

This method is very simple and convenient, therefore it can be widely utilized to the synthesis of the medicinally important compounds which have this chiral synthon (ref. 7).

EXPERIMENTAL PROCEDURE

To a solution of **2a** (1.00 g, 5.46 mmol), (ref. 4) in 10 ml of DMF, a solution of NBS (1.95 g, 10.9 mmol) was added at 0°C and then for 24 hours at room temperature. It was diluted with 400 ml of EtOAc and partitioned. The EtOAc solution was washed with sat. $NaHCO_3$ solution (50 x 3 ml), and sat. NaCl solution (50 x 2 ml), and dried over anhyd. $MgSO_4$. Filtration and evaporation gave crude bromolactones to which 55 ml of 6N-HCl was added. After the reaction mixture was refluxed for 24 hours, it was diluted with 55 ml of sat. NaCl solution and extracted with EtOAc (55 x 3 ml). The combined EtOAc solution was washed with

H_2O (30 x 2 ml) and dried over anhyd. $MgSO_4$. Filtration and evaporation gave (R)-α-methyl β-bromo-α-hydroxy acid, (S) (-)-**4a**, as a white solid (603 mg, yield 91 %) showing 97 % ee (ref. 6). The **2b**, **2c** and **2d** were treated in the same manner as 2a to give the corresponding (S)-α-substituted β-bromo-α-hydroxy acids; (S)-**4b**, (S)-**4c**, and (S)-**4d**, respectively. The results are summarized in Table 1.

ACKNOWLEDGEMENTS

We thank Korean Scientific Foundation (IBRD, 1985, Chem. 3-17) and Research Center for New Drug Development (1990) for financial supports.

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4. (S)-2 are obtained by N-acylation using diethyl phosphorocyanidate (DEPC) (ref. 5), followed by hydrolysis. The results are summarized as follows.

	mp (°C)	$[\alpha]_D^{20}$ ($CHCl_3$)	yield (%)
2a	105-106	- 137.6^0	76
2b	104-105	- 127.3^0	80
2c	caramel	- 99.3^0	75
2d	110-111	- 99.2^0	92

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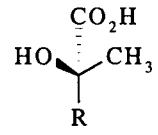
6. The % ee and absolute configuration are determined by correlation of 4b, 4c and 4d with (S)-α,α-disubstituted α-hydroxy acids 5b, 5c and 5d obtained from debromination of parts of the bromolactones (3b, 3c and 3d), followed by hydrolysis (ref. 7).



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SUBSTRATE-SPECIFIC REACTIONS OF DIBROMIDES OF α-ARYLIDENE-BENZOCYCLANONES WITH AZIDE NUCLEOPHILE

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INTRODUCTION

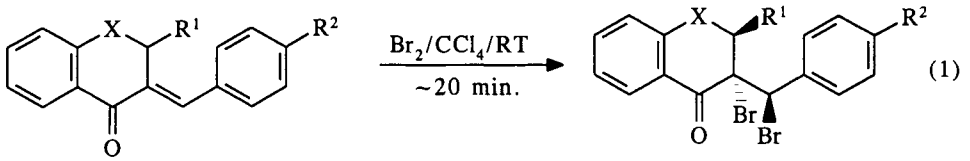
Chalcone dibromides are advantageous intermediates for the preparation of various nitrogen-containing heterocycles (refs. 1-4). In the case of exocyclic α,β-unsaturated ketones, however, only few examples are known concerning the utilization of their dibromides for such purposes (ref. 5). Our aim was, therefore, the synthesis of the dibromides of various exocyclic α,β-unsaturated ketones (ref. 6) and to study their chemical transformations. In our present paper the reaction of such dibromides with azide nucleophile is reported.

RESULTS AND DISCUSSION

The exocyclic α,β-unsaturated ketones **1a-h** used for the preparation of dibromides **2a-h** were E isomers synthesized by known procedures (refs. 7,8). Previously we reported the synthesis of some dibromides (**2a,d,g**) used here as starting materials, by the bromine addition of the appropriate α,β-unsaturated ketones (**1a,d,g**) (ref. 6). In the case of our present study, compounds **1b,c,e,f,h** were allowed to react with a small excess of bromine in carbon tetrachloride solution at room temperature for approx. 20 min. to afford the dibromides **2b,c,e,f,h** (Eqn. 1) (Table 1).

Structure and stereochemistry of the dibromides **2a-h** were elucidated by various NMR methods including 1D proton-proton NOE difference spectra and 2D

heterocorrelation measurements as well. Since the bromine addition is probably an anti-type electrophilic addition



(1)

1 a-f 2 a-f

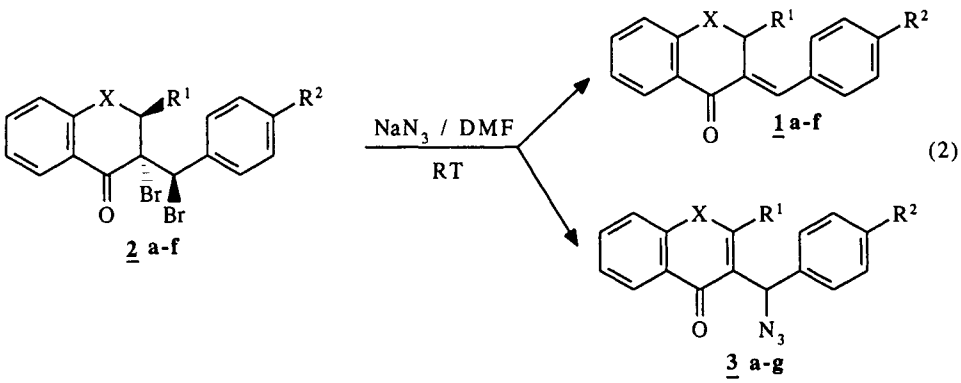
Table 1. Yields of bromination of exocyclic α-β-unsaturated ketones

	X	R^1	R^2	Yield (%)
a	O	H	H	78.4
b	O	H	Me	79.2
c	O	H	Cl	78.6
d	S	H	H	75.6
e	S	H	OMe	73.0
f	S	H	Me	85.9
g	O	Ph	H	70.2
h	O	Ph	Cl	69.1

(ref. 9), racemic mixtures with 3R,C_α-S and 3S,C_α-R configurations are obtained in the case of **2a-f**. Owing to the presence of three centres of chirality, this bromine addition may result in the formation of diastereomeric mixtures of compounds **2g** and **2h**. NMR studies proved that under the reaction conditions used, however, no diastereomeric mixture was obtained starting from **1g** and **1h**, consequently the reaction providing dibromides **2g** and **2h** is highly stereoselective. The reason for this stereoselectivity and the conformation of dibromides synthesized have been discussed in detail in our previous paper (ref. 6).

Treatment of dibromides **2** with sodium azide in N,N-dimethylformamide (DMF) at room temperature resulted in the formation of two products, 3-(α-azidobenzyl)chromones **3a-c,g** or -1-thiochromones **3d-f** and the 3-arylidenechromanones **1a-c,g,h** or -1-thiochromanones **1d-f**, respectively (eqn. 2). As shown by yield data given in Table 2, the substituent at position 2 plays decisive role in the product ratio. Dibromides unsubstituted at position 2 tended to give almost exclusively azides **3a-f** and only a small amount of **1** was obtained. On the contrary, the reaction of flavanone derivatives **2g,h** gave 3-arylideneflavanones

1g,h as major product in a longer reaction. 3-(α-Azido-benzyl) flavone (**3g**) was isolated as a small minor product from the reaction mixture of **2g**



(2)

Table 2. Yields in the treatment of dibromides **2** with azide

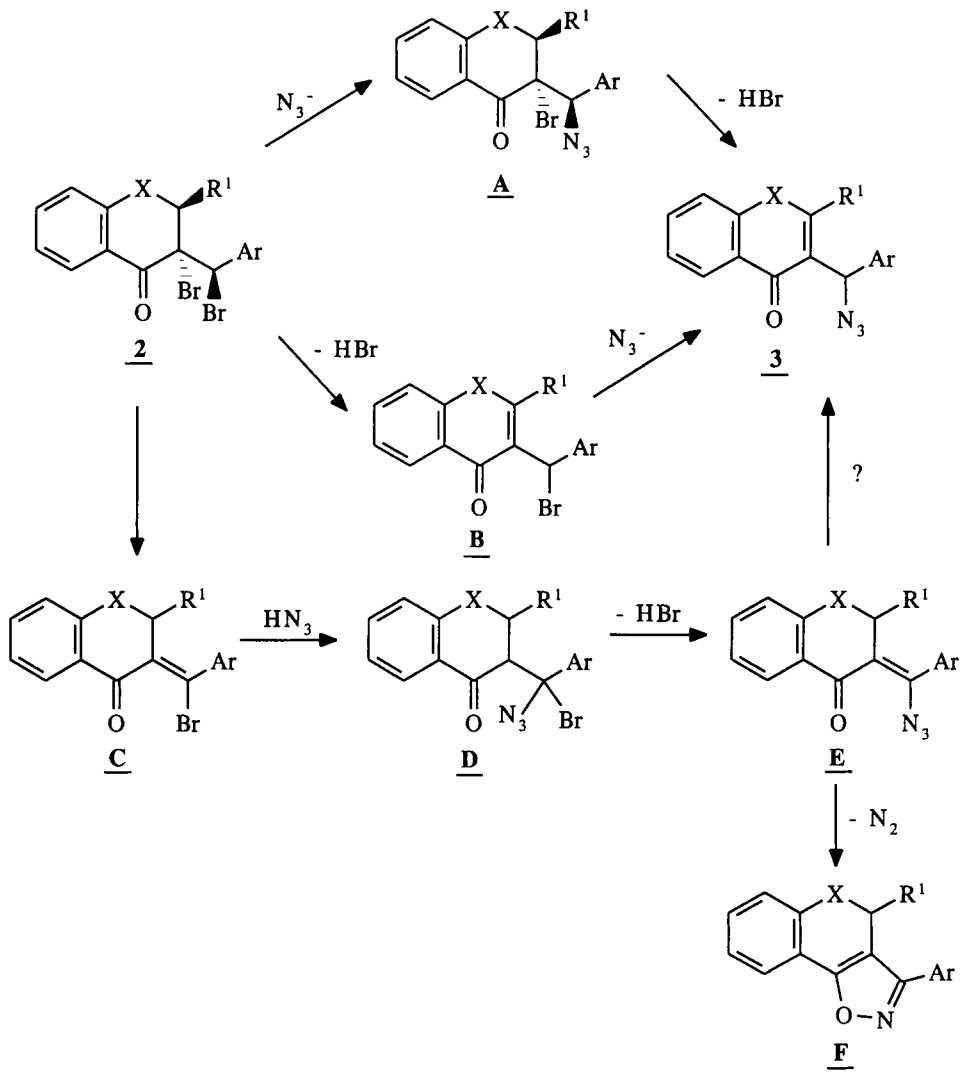
				Yield (%)	
	X	R^1	R^2	**3**	**1**
a	O	H	H	92.0	0.8
b	O	H	Me	78.1	3.6
c	O	H	Cl	85.0	1.0
d	S	H	H	83.3	3.2
e	S	H	OMe	77.5	1.8
f	S	H	Me	75.3	3.4
g	O	Ph	H	2.3	76.0
h	O	Ph	Cl	0	70.6

but no azide **3h** could be detected in the transformation of **2h**.

Surprisingly, no marked effect of the substituent R^2 on the product ratio was observed whereas in the similar reaction of 2'-hydroxychalcone dibromides a great influence of substituent R^2 on the competing reaction pathways was found (ref. 4). Noteworthy, no formation of the azide E (regioisomer of **3**) was detected.

Azides **3a-g** were characterized by their elemental analysis, IR, ^1H and ^{13}C NMR spectra (including INAPT measurements to support the assignations of ^{13}C NMR spectra) and MS data.

Chromones **3a-c,g** were found to show separated νC = 0 and νC = C bands at ~ 1640 and ~ 1620 cm^{-1}, respectively, whereas 1-thiochromones **3d-f** had coalesced



Scheme 1. Possible routes leading azide **3**

νC = O and νC = C bands between wavenumbers 1610-1615 cm^{-1}. Characteristic ^1H NMR signals of chromones **3a-c,g** were 8.15-8.20 (dd, H-5), 7.90-7.95 (d, H-2) and ca. 6.00 ppm (d, H_α), the respective chemical shifts for 1-thiochromones **3d-f** were ca. 8.5, 7.95-8.00 and 6.10-6.20 ppm. Both series had a small characteristic long-range coupling between H-2 and H_α with a coupling constant ca. 1 Hz. In their ^{13}C NMR spectra C-4 signals ranged between 175 and 178 ppm, whereas C_α appeared at 60 ppm in the case of chromones and at 63 ppm in the case of 1-

thiochromones. As a characteristic MS feature, neither compound had molecular peak but all of them showed an intensive M-28 (loss of nitrogen from the azido group). Their base peak were the appropriate chromone/1-thiochromone molecular ion.

The possible routes leading to azides **3** are outlined in Scheme 1. The only pathway which we can exclude the **2**⇒**C**⇒**D**⇒**E**⇒**3** sequence since neither intermediate **E** nor its possible derivative **F** could be detected in the reaction mixture. (β-Azido α,β-unsaturated ketones are known to afford isoxazoles via nitrenes derived by loss of nitrogen (refs. 4,10). Azides **3** may form either via intermediate **A** (S_N + E route) or via allyl bromide-type intermediate **B** (E + S_N route), both routes may operate on the basis of experimental results obtained so far.

Dehalogenation of dibromides **2** affording 3-arylidenchromanones **1a-c,g,h** or -1-thiochromanones **1d-f** may be rationalized by an attack of the nucleophile on a bromine atom instead of hydrogen. This process is well documented in the field of chalcone dibromides (refs. 11-17) though it has been reported to take place usually in the presence of soft nucleophiles, such as iodide ion (ref. 12), thiourea (ref. 13), hydrogen sulfide ion (ref. 14), hydrogen selenide ion (ref. 15), stannous chloride (ref. 16) or pyridine (ref. 17). In the reaction of 2'-hydroxychalcone dibromides with azide ion debromination was observed only in the presence of 4'-methoxy group and it was only a side reaction with small participation (ref. 4).

Further studies to clarify the mechanism and to investigate the synthetic use of azides **3** are in progress.

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ORGANOBROMINE COMPOUNDS IN REACTIONS OF HOMOLYTIC ADDITION AND TELOMERIZATION

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This paper reviews the recent studies in the field of radical reactions of organobromine compounds. A special attention is paid to the use of metal-complex systems based on iron pentacarbonyl as catalysts; this makes it possible to perform the initiation and chain transfer reactions selectively at C-Br bond.

The first examples of stereo-controlled radical addition and telomerization reactions are discussed.

INTRODUCTION

Radical reactions proceeding with cleavage of C-Br bond have been studied to a lesser extent than the similar processes of organochlorine compounds, however, the easier homolysis of C-Br bond and the high reactivity even a single bromine atom in a molecule in various reactions provide a great potential for synthesis of diversified polyfunctional organic compounds. Organic bromides readily enter into radical reactions of addition and telomerization; they actively generate radicals at the step of initiation, and at the step of chain transfer their reactivity is attributed to the easier electron transport in transition state than that for chlorides (because of high polarizability of C-Br bond). This determines a wide choice of initiators and initiating actions, which can be used : peroxides, azocompounds, radiation, oxidative-reductive systems, and natural light in some cases.

The essential difference in chemical behavior of chlorides and bromides used as telogens (addends) can be distinctly seen when the reactions of chloro- and bromoacetates are compared. In addition and telomerization reactions monochloroacetates react with 1-alkenes exclusively at C-H bond [under initiation

with azobisisobutyronitrile (AIBN)]; and monobromoacetates react involving C-Br bond cleavage.

The results of experiments in which the individual compounds were isolated, show that the more halogen atoms are at the carbon atom bearing bromine, the more reactive this compound is in reactions of addition and telomerization both at step of initiation and at step of chain transfer. Homolysis of C-Br bonds can also be activated by electron-withdrawing substituents (for instance, an ester group) at α-position to the reacting bromine atom. Therefore, esters of bromosubstituted acetic and malonic acids are more active in radical reactions than polybromomethanes, containing the same number of bromine atoms. Of the studied bromine-containing compounds, CBr_4 and CCl_3Br were the most reactive. The reactions involving these compounds can occur at temperatures close to room ones; the optimum conditions are 50-70°C. Dibromodichloromethane is sufficiently active in radical reactions. Of hydrogen-containing polybromomethanes, bromoform is quite reactive, it reacts exclusively with cleavage of C-Hal bond (unlike $CHCl_3$), regardless of initiation conditions. However, a character of proceeding side and secondary reactions is determined by the nature of initiating system (see below).

The less efficient dibromomethane also reacts presumably with C-Br bond rapture, although some examples of reacting at a C-H bond are known (ref. 1).

Non-activated *n*-alkylbromides react non-selectively under radical conditions, because the radicals formed at the step of chain growth, actively abstract hydrogen atoms from bromoalkane alkyl chain.

The high efficiency of bromine-containing compounds in homolytic processes allows us to involve in reactions with them not only common monomers, but those which can be easily polymerized (vinyl chloride, acrylates, styrene, etc.) to yield individual adducts or, in some cases, a mixture of the lower telomers. Vinylene carbonate proved to be a very interesting and promising monomer of those studied, excepting the examples reported below (Table 1) : the reaction of bromomethanes with vinylene carbonate opens a simple route to the synthesis of carbohydrates (ref. 2). The use of functional-substituted monomers in reactions of addition and telomerization with organobromine compounds (taking into account the following replacement of bromine by other groups) allows us to obtain polyfunctional compounds with various length of a carbon chain.

Acetylenes are of little promise in such reactions, because they require fairly drastic conditions, that is not compatible with the high explosion hazard of acetylenes. The reactions with dienes are often proceed unambiguously (1,2- and 1,4-addition) that makes it difficult to isolate individual compounds.

The adducts containing di- and tribromomethyl groups can react with another molecule of monomer, i.e. the secondary reactions occur including step-by-step telomerization in this case. The presence of the bromine atom adjacent to the radical center makes it probable the fragmentation with ejection of the bromine atom, which starts the further reaction, and as a result, the products of bromine addition to a double bond, not adducts, are formed.

Finally, concurrently with addition, reduction of tri- or dihalomethyl groups in the adduct can occur under conditions of initiating by metal-complex systems in the presence of hydrogen donor; chain transfer at C-H bond, at C-Br one, is also possible to form compounds containing one bromine atom less than adducts.

In this prezentation we consider the data published within recent 6 - 7 years, because the works reported previously are surveyed sufficiently completely in monograph "Radical Telomerization" (ref. 3).

The new examples of radical reactions of organobromine compounds, described in recent years are presented in Table 1.

REACTIONS OF TETRABROMOMETHANE

Within the recent years a number of interesting new data on the reactions with CBr_4 have been reported. This is associated with using the initiators uncommon for the reactions of this type as well as extension of the list of monomers involved in the reactions with CBr_4.

Addition of CBr_4 to a number of monomers including functional-substituted monomers (heptene-1, octene-1, styrene, and methylacrylate) has been performed in the presence of SmJ_2 under mild conditions to give the adducts in high yield (ref. 4).

The authors conduct the reaction using 5 - 10 % SmI_2 in acetonitrile solution at 60°C for several hours, then the temperature is decreased to room one. The yield of the adducts reaches 80 %. A general scheme of the reaction the authors presented (taking into account a possibility of using other polyhalomethanes) includes the formation of intermediate initiating complex followed by chain transfer by the radical-adduct to the starting polyhalomethan.

$$Y\text{-}C\text{-}X_3 \xrightarrow{SmI_2} [Y\text{-}C\text{-}X_3]^{\cdot-}SmI_2^{+} \qquad (A)$$

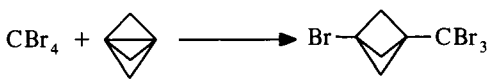
$$(A) \longrightarrow SmI_2Y + \dot{C}CX_3$$

$$\dot{C}X_3 + CH_2{=}CHR \longrightarrow \dot{C}X_3\text{-}CH_2\text{-}CHR \qquad (B)$$

$$B + Y\text{-}C\text{-}X_3 \longrightarrow CX_3\text{-}CH_2CHYR$$

The compounds of trivalent samarium (SmI_2Y) do not take part in chain transfer; probably, the further conversion $Sm^{+3} \longrightarrow Sm^{+2}$ requires a stronger reducing agent. This is the essential distinction of this reaction from the similar processes initiated by $Fe(CO)_5$, for example, in which the intermediate iron complex containing halogen is capable of participating in the step of chain transfer (halogen is transferred from the complex to the adduct-radical); after this Fe^0 particle is formed, capable of entering in the reaction again (ref. 3).

Tetrabromomethane reacts virtually instantly with 1,1,1-propellane to give corresponding adduct (ref. 5).



The reaction occurs at room temperature, does not require even lighting, and gives the adduct in a high yield. A radical character of the process is confirmed by the presence of the appropriate signals in ESR spectrum, and it is in a good agreement with the products of the reaction formed.

The easy homolysis of C-Br bond in CBr_4 allowed us to conduct the radical chain reaction of CBr_4 with 3,3,3-trifluoropropene under common conditions (benzoyl peroxide), although in this case the strong electrophiles are used as reagents (an addend and a monomer), i.e. a very unfavorable combination of polar factors for proceeding the process takes place (ref. 6).

$$CBr_4 \xrightarrow{Bz_2O_2} \dot{C}Br_3$$

$$\dot{C}Br_3 + CH_2{=}CHCF_3 \longrightarrow CBr_3CH_2\dot{C}HCF_3$$

The occurrence of the CF_3 group adjacent to the radical center gives the radical a strongly electrophilic character; and only the energetically easy homolysis of C-Br bond in CBr_4 allows us to conduct the following process as a chain one.

$$A + CBr_4 \longrightarrow$$
$$\longrightarrow CBr_3CH_2CHBrCF_3\ (T_1) + \dot{C}Br_3\ (chain)$$

Nevertheless, such a combination of polar factors actually makes this step less efficient than that is usually in the reactions with CBr_4, and as a result the radical-adduct $CB_3CH_2CHCF_3$ takes part in concurrent reaction of growth chain with another monomer molecule to form telomer T_2; this is basically non-typical for reactions of CBr_4.

$$CBr_3CH_2\dot{C}HCF_3 + CF_3CH{=}CH_2 \longrightarrow$$
$$\longrightarrow CBr_3CH_2CH(CF_3)CH_2\dot{C}HCF_3$$

$$C + CBr_4 \longrightarrow$$
$$\longrightarrow CBr_3CH_2CH(CF_3)CH_2CHBrCF_3 + \dot{C}Br_3 \text{ etc.}$$

The structure of telomers T_1 - T_3 is confirmed by ^{13}C NMR spectra recorded for individual compounds.

Conducting of this reaction under the strictly controlled conditions and within a wide range of reagents ratio allowed to estimate partial chain transfer constants /$C_n = K_{tr}/K_{gr}$/ for the first three growing radicals (C_1 = 14, C_2 = 64; C_3 = 60), i.e. a chain transfer (K = t2) by growing radicals occurs more efficiently than growth (K = g2) does. It is interesting to notice that the similar values of constants were also obtained previously in the reaction of CBr_4 with vinyl chloride (ref. 7), although these monomers are essentially differ in their properties (vinyl chloride can be easily polymerized, but it is not typical for trifluoropropene). We shall see below that decrease in efficiency of an addend as a reaction chain transfer agent (for instance, transfer from CBr_4) makes these reaction different to an essential extent in both chemical and kinetic results.

Some authors have studied the reaction of CBr_4 with vinyl chloride. Under common conditions, this reaction proceeds as telomerization to form substantially the first two telomers : $\mathbf{CBr_3(CH_2CHCl)_nBr}$ (n = 1, 2); only in the cases, when monomer-telogen ratio is sufficiently high, noticeable amount (to 10 %) of the third telomer (T_3) is formed (ref. 7). Structure of telomers T_1 - T_3, isolated as individual compounds. In the first work on studying the relative kinetics of this reaction the quantitative composition of the mixture of telomers was estimated by TLC method (ref. 8). The authors obtained the values of chain transfer constants less than 1 (0.33), which we consider as low-probable data, taking into account the high

efficiency of CBr_4. These results were reexamined later using GLC technique for quantitative analysis (ref. 7). In this case the authors obtained $C_1 \sim 14.6$; $C_2 \sim 73.5$; this results seem to correlate to a greater extent to actual reactivity of the reagents.

REACTIONS OF TRIBROMOMETHANE (BROMOFORM)

Homolysis of the C-Br bond in bromoform occurs more difficult than that in CBr_4, this determines a number of specific features of the processes. In some cases the use of the efficient methods of initiating (including with metal complexes) and comparatively drastic conditions of the reactions are required. Rather small differences in nature of reagents affect the results of the reactions to more obvious extent; the role of polar effect increases in determination of a character of reaction with $CHBr_3$. For example, unlike CBr_4, the reactions of $CHBr_3$ with $CH_2=CHCl$ and $CF_3CH=CH_2$ proceed in different manners; in some cases nonselective reactions are observed under common conditions of initiation. In constrast to CBr_4, the reaction of bromoform with propellane requires radiation (hν, 20-30°C, 1.5 h) (ref. 5) :

In this case addition occurs fairly effectively to give the adduct in 88 % yield, and formation of telomers was not observed. The presence of the mobile bromine atom at the tertiary carbon atom makes these compounds interesting and promising synthons for further chemical transformations.

As was noted above, the less effectivity of $CHBr_3$ (in comparison with CBr_4) as a chain transfer agent of the reaction reveals in appearing the compounds (in the reaction mixtures), caused by occurring competitive reactions, in which intermediate radicals are involved. The reaction of $CHBr_3$ with 3,3,3-trifluoropropene is illustrative in this respect, in which a character of the reaction products and composition of the reaction mixture depend on method of initiating, to an essential extent (ref. 19). The studies showed that the reaction of 3,3,3-trifluoropropene with $CHBr_3$ in the presence of benzoyl peroxide as an initiator proceeded in a fairly complicated manner to form a mixture of compounds containing from two to four bromine atoms. In this case in addition to telomers of normal structure, the compounds are formed, the appearance of which are

associated with the fact that intermediate radicals take part in hydrogen transfer reactions, rearrangements, reaction of addition of the other molecule of monomer or bromine transfer reactions.

The authors (ref. 19) managed to perform this reaction selectively as telomerization at the C-Br bond of bromoform using initiating system $Fe(CO)_5$ + DMF, which facilitates a bromine transfer at a step of a chain transfer (ref. 19). In this case only one row of telomers is formed which contain three bromine atoms in molecules :

$$CHBr_3 \xrightarrow{Fe(CO)_5 + DMF} \dot{C}HBr_2$$

$$\dot{C}HBr_2 + CH_2{=}CHCF_3 \longrightarrow CHBr_2(CH_2CHCF_3)^{\bullet}_n$$

$$CHBr_2(CH_2CHCF_3)^{\bullet}_n \xrightarrow{DBr} CHBr_2(CH_2CHCF_3)_n Br \quad n = 1 - 3$$

All the products were isolated as individual compounds, their structures are confirmed by ^{13}C NMR method (Table 1). Monograph (ref. 3) discusses in detail a character of action of metal-complex initiating system in radical reactions of polyhalogenmethanes with unsaturated compounds.

The use of metal-complex initiating systems proved to be especially promising in carrying out the reactions with acrylic monomers which can be easily polymerized, when the common initiators of radical reactions are excepted. The use of $Fe(CO)_5$ + DMFA system allows us to perform homolytical addition of bromoform to acrylic monomers selectively at C-Br bond with no essential polymerization (ref. 10).

$$CHBr_3 + CH_2{=}CRX \xrightarrow{Fe(CO)_5 + DMF} CHBr_2CH_2CRBrX$$

$R = H$, $X = CN$, $COOCH_3$; $R = CH_3$, $X = COOCH_3$

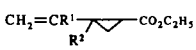
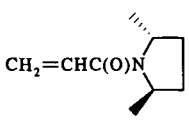
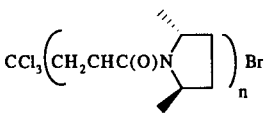
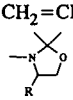
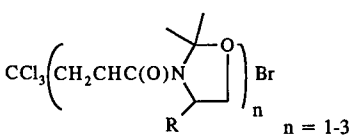
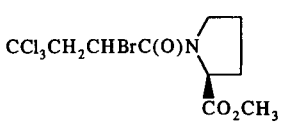
The structure of the adducts obtained (addition resulted from homolysis of C-Br bond) is an indirect evidence for radical character of the process. Ionic addition of haloforms is known to occur at C-H bond (ref. 11), this leads to adducts with CX_3 group. The highest yield of the adduct with bromoform was obtained for

methylmetacrylate (78 % with respect to the reacted $CHBr_3$); the yields are essentially lower for acrylonitrile and methylacrylate (25 and 15 %, respectively).

The radical addition of bromoform to ketensilylacetals has been described, initiated with AIBN or Et_3B (ref. 12). The reaction yields polyfunctional silicon-containing compounds of $CHBr_2C(R)CBr(OR^2)OSiR^3$ type or products of their conversions (hydrolysis, fragmentation of R^2 etc.).

Table 1. Radical reactions of organobromine addends with unsaturated compounds

Addend	**Monomer**	**Reaction conditions**	**Adducts, telomers / Yield / C_n**	**Ref.**
CBr_4	$CH_2=CHCl$	Bz_2O_2	$CBr_3(CH_2CHCl)_nBr$; n = 1 - 3; C_1 = 14,6; C_2 = 73,5.	7
	$CH_2=CHCF_3$	Bz_2O_2	$CBr_3(CH_2CHCF_3)_nBr$; n=1-3; C_1=15; C_2=64; C_3=60	6
	$CH_2=CHR$	SmI_2, 60°	$CBr_3CH_2CH(R)Br$ /30-75/	4
	R=Bu, C_6H_{13}, Ph, CO_2CH_3			
		room temp.	CBr_3  Br /high yield/	3
$CHBr_3$	$CH_2=CHCN$	$Fe(CO)_5$ + DMF 95-100°, 2 h	$CHBr_2CH_2CHBrCN$ /25/	10
	$CH_2=CHCO_2CH_3$	" "	$CHBr_2CH_2CHBrCO_2CH_3$ /78/	10
	$CH_2=C(CH_3)CO_2CH_3$	" "	$CHBr_2CH_2C(CH_3)BrCO_2CH_3$ /15/	10
	$CH_2=CHCF_3$	Bz_2O_2	$CHBr_2(CH_2CHCF_3)_nBr$, n=1,2	9
			$CBr_3CH_2CHBrCF_3$, $CBr_3CH_2CH(CF_3)CH_2CHBrCF_3$	
			$CHBr_2CH_2CH(CF_3)CH_2CH_2CF_3$	
			$CBr_3CH_2CH(CF_3)CH_2CH_2CF_3$	
	$CH_2=CHCF_3$	$Fe(CO)_5$ + DMF, 100°	$CHBr_2(CH_2CHCF_3)_nBr$ n=1-3	9
		20-30°, 1,5 h.	$CHBr_2$  Br /88/	5
CH_2Br_2	$CH_2=CHCF_3$	$Fe(CO)_5$ + DMF, 145°	$CH_2Br(CH_2CHCF_3)_nBr$; n=1,2	9
CCl_2Br_2	$CH_2=CHCl$	Bz_2O_2, 60°	$CCl_2Br(CH_2CHCl)_nBr$; n=1-3; C_1=7,7; C_2=54,3	7

Addend	Monomer	Reaction conditions	Adducts, telomers / Yield /	Ref.
CCl_3Br	$CH_2=C(CH_3)CO_2R$; R=i-Pr, t-Bu	50 - 90°	$CCl_3(CH_2C(CH_3)CO_2R)_nBr$, n=1-3	13
	$CH_2=CHR$; R=Bu, C_6H_{13}, Ph, CO_2CH_3	SmI_2, 60°	CCl_3CH_2CHRBr /30-70/	4
		AIBN	$CCl_3[CH_2C(R^1)=C(R^2)CH_2CHCO_2C_2H_5)_nBr$	15
	$R^1 = R^2 = H, CH_3$		n = 1 - 3, $C_n \approx 1$	
		20°		14
	 (2R,5R)	hv	 n=1-5; C_2-C_5≈0,3-0,5	16
	$CH_2=CHC(O)$  R=Ph, i-Pr	hv	 n = 1-3	17
	$CH_2=CHC(O)$  (2S)	$Fe(CO)_5$ + $P(C_6H_5)_3$ 75°, 2 h	 /80/	18
$C_6H_5CH_2Br$	$CH_2=CH_2$	$Fe(CO)_5$ + DMF (HMPA)	$C_6H_5CH_2CH_2CH_2Br$	19
	$CH_2=CHC_4H_9$	140°	$C_6H_5CH_2CH_2CHBrC_4H_9$	19
	$CH_2=CHSi(CH_3)_3$	" "	$C_6H_5CH_2CH_2CHBrSi(CH_3)_3$	19
	$CH_2=CHCF_3$	" "	$C_6H_5CH_2(CH_2CHCF_3)_nBr$, n = 1,2	19, 21, 22
	$CH_2=CHCO_2CH_3$	" "	$C_6H_5CH_2CH_2CHBrCO_2CH_3$	19
	$CH_2=CHCN$	" "	$C_6H_5CH_2CH_2CHBrCN$	19, 27
	$CH_2=CHCN$ + $CH_2=CHSi(CH_3)_3$	" "	$C_6H_5CH_2CH_2CHBrCN$, $C_6H_5CH_2CH_2CHBrSi(CH_3)_3$ $C_6H_5CH_2CH_2CH(CN)CH_2CHBrSi(CH_3)_3$	27
	$CH_2=CHCl$	" "	$C_6H_5CH_2(CH_2CHCl)_nBr$, n = 1,2	20

Addend	Monomer	Reaction conditions	Adducts, telomers / Yield /	Ref.
$BrCH(CO_2CH_3)_2$		hv	$(CH_3O_2C)_2CH$  Br /69/	5
$BrCF_2CFClBr$	$CClF=CF_2$	UV	$Br(CF_2CClF)_n(CClFCF_2)_m$ Br n=m=1; n=1, m=2; n=2, m=2	28
BrCN		hv	NC ()$_n$Br n=2,3	14
$CF_2=NBr$	$CF_2=CFX$, X=F, Br	hv	$CF_2=NCF_2CFBrX$ /82, 67/	29

REACTIONS OF DIBROMOMETHANE (METHYLENE BROMIDE)

Methylene bromide is essentially less effective in radical reactions as a chain transfer agent; as a result, the reactions with methylene bromide proceed non-selectively and with small conversion of starting substrate.

It is natural that in this case very drastic conditions and the most efficient initiating systems are required. Conducting the reaction of CH_2Br_2 with 3,3,3-trifluoropropene has recently come as new success. It should be noted that even the system $Fe(CO)_5$ + DMF is used at 140-145°C, the reaction occurs with a small conversion and obtaining a complex mixture of products, in which telomers of formula $CH_2Br(CH_2CHCF_3)_nBr$ predominate, formed as a result of cleavage of C-Br bond in telogen. The authors isolated the first two telomers (n = 1,2) as individual compounds; the structure is supported by ^{13}C NMR spectra.

REACTIONS OF BROMOCHLOROMETHANES

The estimation of reactivity of polyhalomethanes in the reactions with the same monomer shows that the quantity of halogen atoms in a molecule is the most essential factor affecting the easiness of homolysis of even one C—Br bond in molecule, and the influence of the halogen nature (chlorine or bromine) is of less significance. For instance, the analysis of the data on relative kinetics of some polyhalomethanes reactions with vinyl chloride allows us to grade the studied polyhalomethanes according to their reactivity, as follows :

$$CBr_4 > CCl_2Br_2 > CCl_3Br > > CHBr_3$$

Polybromochloromethanes containing two or even one C—Br bond are thus seen to be more efficient chain transfer agents than bromoform with three bromine atoms in molecule.

Of bromochloromethanes reacting mainly at C—Br bonds, bromotrichloromethane has been the most investigated compound. Both the various monomers and diversified routes of initiations were used in the studies of CCl_3Br. The addition of bromotrichloromethane to α-olefines under common conditions of radical initiation has been described by a number of examples (ref. 3).

The use of two-valence samarium salts is a radically new approach both for CCl_3Br and CBr_4, which actively initiate these reactions under mild conditions (ref. 4) :

$$CCl_3Br + CH_2{=}CHR \xrightarrow[60\,^\circ C,\ 10\ h.]{SmJ_2,\ MeCN} CCl_3CH_2CHBrR \quad (\text{yield } \sim 80\ \%)$$

$R = C_4H_9,\ C_6H_{13},\ Ph,\ CO_2Me$

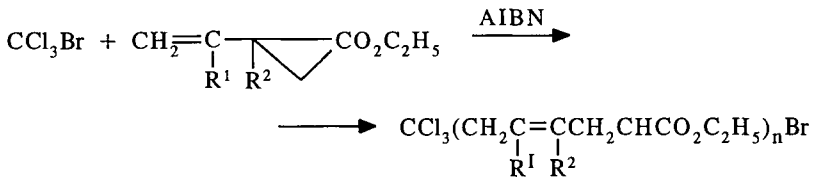
As in the case of CBr_4, the authors suppose the mechanism of one-electron transfer involving the complex particle $[BrCCl_3]^{\cdot-}\ SmI_2^+$ (possibly, it is a charge transfer complex), which generates $\dot{C}Cl_3$ radical leading a chain. Despite the high efficiency of $\dot{C}Cl_2Br$ as a chain transfer agent, its reactions with easily polimerizable esters of methacrylic acid proceed as the telomerization resulting in the unexpectedly large fraction of the higher telomers containing two or three monomeric units (ref. 13).

$$CCl_3Br + CH_2{=}CMeCOOR \xrightarrow{50\ -\ 90^\circ} CCl_3(CH_2CMeCO_2R)_nBr$$

$R = Me_2CH,\ Me_3C$ $\qquad$ $n = 1\ -\ 3$

At the same time, the reaction of CCl_3Br with 1,1,1-propellane gives mostly the adduct, even when the propellane excess is used (ref. 14) :

The reaction of bromotrichloromethane with alkenylcyclopropanes (ref. 15) is of interest from the synthesis of polyfunctional compounds standpoint.

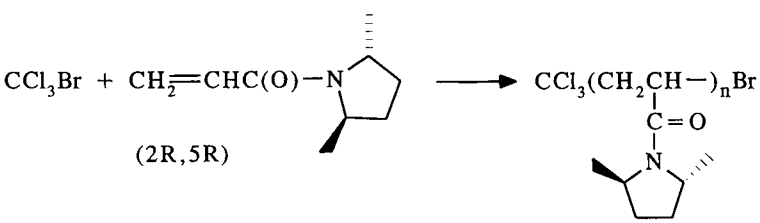


R_1, R_2 = H, CH_3, n = 1 - 7

The studies of configuration showed that telomers were formed predominantly as E-form. The data of relative kinetics show that the partial chain transfer constants for telomer radicals are close to one and do not change virtually as the length of the radical chain grows.

This is natural, because in this case even in the first growing radical (n = 1) CCl_3 group is sufficiently far removed from the radical center and does not affect practically its reactivity, which is mainly determined by neighborhood of $COOC_2H_5$ groups for all growing radicals. The value of the partial constants C_n, close to 1, reflects the equal probability of the chain transfer and chain growth reactions for the growing radical.

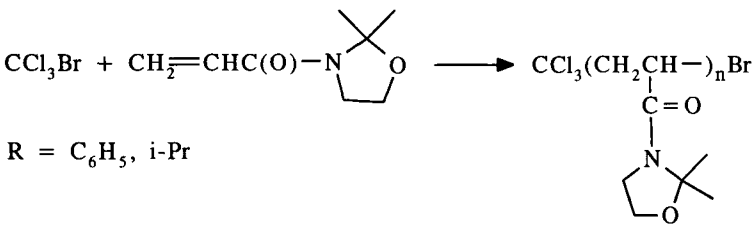
A set of works has been recently published, which show the possibility of stereochemical control in the processes of radical additions and telomerization. Photochemical telomerization of bromotrichloromethane with chiral 2,5-dimethyl-pirrolidine acrylamide has been described (ref. 16) :



The first five telomers (n = 1 - 5) were isolated and identificated. The authors showed that telomers T_2 and T_3 are preferentially formed in one stereoisomeric form (with minor amounts of other possible isomers), i.e. the radical addition reaction makes it possible to perform asymmetric control at the steps of chain transfer and chain growth. The partial chain transfer constants C_n are given in this work, which are within the range from 0.3 to 0.5 for radicals C_2-C_5. We consider

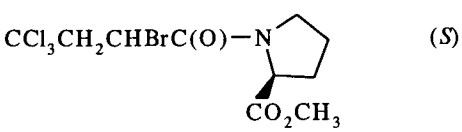
these values as underestimated. The quantitative assessment of the telomers ratio can be performed only quite approximately, as judged from the chromatograms (liquid and gel-permeation chromatography), presented in this work. This makes the determination of constants to be quite unreliable.

Addition of bromotrichloromethane to substituted N-acryloyloxazolidines is also sufficiently selective stereochemically (ref. 17).



Stereospecificity of this reaction reaches 15:1 for telomer T_3. Telomer T_3 is a crystalline product, this allowed the authors to use X-ray diffraction analysis for studying stereochemistry. Stereoselectivity observed in the formation of T_3 shows that both addition step and the step of halogen transfer to the growing radical proceed stereoselectively in this case.

One more example of the similar reaction is the addition of bromotrichloromethane to (S)-1-acryloyl-2-methoxycarbonylpirrolidine catalyzed with system [$Fe(CO)_5$ + PPh_3] (75°C) (ref. 18). In this case the authors managed to exclude telomerization virtually and obtain adduct in 80 % yield, which is one of two possible diastereomers.



(*S*)

Thus, this first example of stereoselective radical reaction, initiated with the system based on $Fe(CO)_5$, shows opportunities and prospects of using the metal complex initiators for obtaining the stereomerically pure adducts of bromine-containing compounds to vinyl monomers with chiral substituents.

Dibromodichoromethane was studied as telogen in the reaction with vinyl chloride (ref. 7). The authors showed that the reaction occurred as telomerization (under usual conditions) ; the changes in monomer / telogen ratio (from 1.5 to 15) allowed to vary the adduct content from 80 to 30 %.

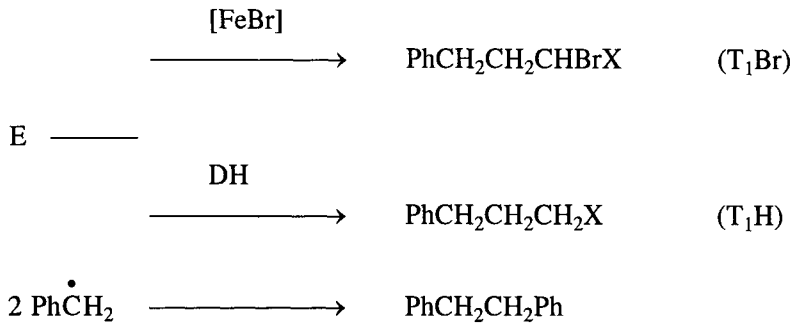
The first three telomers $CCl_2Br(CH_2CHCl)_nBr$ (n = 1 - 3) were isolated as individual compounds, the structure was confirmed by ^{13}C NMR spectroscopic data. The values of the chain transfer partial constants (C_1 = 7; C_2 = 54.3) point to the high efficiency of CBr_2Cl_2 as a chain transfer agent, which comparable with that of CBr_4 (C_2 = 74.2) (in the similar reaction with vinyl chloride) (ref. 7).

REACTIONS OF BENZYL BROMIDE

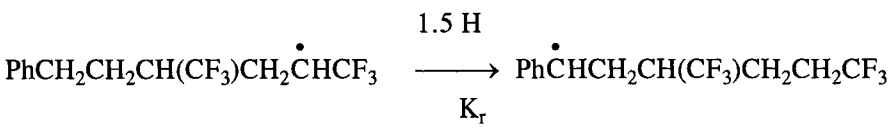
As a rule monobromosubstituted compounds nonactivated with functional groups do not enter into radical reactions under common conditions of peroxide initiation. The selective homolysis of C-Br bond (combined with satisfactory yields of products) can be achieved only in the case of using metal complex initiators. Benzyl bromide is one of such organobromine compounds, which has been widely studied in recent years. The addition of benzyl bromide to styrene had been made earlier in the presence of equimolar amounts of (CuBr + bipyridyl) system under sufficiently drastic conditions. The later studies showed that the most promising initiating systems for the reactions of benzyl bromide with unsaturated compounds were those based on $Fe(CO)_5$. The use of systems $Fe(CO)_5$ + DMF (HMPA) as initiators made it possible to conduct the reactions of benzyl bromide with a wide series of monomers which essentially differ in their polymerizability and polar characteristics of substituents (refs. 19, 20). The addition of benzyl bromide to functional-substituted monomers is a promising route to synthesis of polyfunctional aromatic compounds as well as a convenient model for studying reactivity of benzyl radicals with monomers containing substituents of various polar nature. This prompted the authors to investigate comprehensively the reactions with benzylbromide. Under comparable conditions the authors have studied the addition of benzylbromide to monomers $CH_2=CHX$ (X = H, C_4H_9, $SiMe_3$, Cl, CF_3, COOMe, and CN) using $Fe(CO)_5$ (up to 10 %) as an initiator, combined with DMF or HMPA (refs. 19, 20). The reactions proceed in accordance with a general scheme, as follows :

$$PhCH_2Br \xrightarrow{Fe(CO)_5 + DMF} Ph\dot{C}H_2$$

$$Ph\dot{C}H_2 + CH_2=CHX \longrightarrow PhCH_2CH_2\dot{C}HX \quad (E)$$



At this stage of the research the authors believe that radical-adduct E transfers a chain with abstracting a bromine atom from bromine-containing iron carbonyl complex to give adduct T_1^{Br}. Stabilization of radical E by hydrogen abstraction results in T_1^{H}. The formation of dibenzyl is one of the arguments for the radical character of the reaction, in the authors' opinion. It was noted in this case that the quantity of dibenzyl in the reaction mixture decreases as the monomer concentration increases; and T_1^{Br} is a major product of the reaction for all the monomers. From the monomer activity standpoint, the best results have been obtained with vinyltrimethylsilane, in the case of hex-1-ene the yield was somewhat lower. The authors show that in the latter case the differences in the use of DMF or HMPA as coinitiators was noticeable : if the telogen conversions are almost equal, the yield of the adduct is 2.5 times higher for HMPA than that for DMF. The reaction with monomers containing electron-withdrawing groups (Cl, CF_3, CO_2Me, CN) gives the lower yields of the adducts at high conversion of benzyl bromide. 3,3,3-Trifluoropropene is a compound of special interest in this series. Some transformations of the intermediate telomer radicals had been observed in this case, which prompted to study this reaction in more details. In addition to telomers $C_6H_5CH_2(CH_2CHCF_3)_nBr$ (T_n^{Br}, n = 1,2), the authors have found compound $PhCH{=}CHCH(CF_3)CH_2CH_2CF_3$ and explained its formation by rearrangement of the intermediate radical with two monomer units followed by easy dehydrobromination :



An intramolecular mechanism of the rearrangement has been shown in the special ESR study (refs. 21, 22), conducted on the model radicals, generated by abstraction of a bromine atom from T_2^{Br}; the rate constant K_2, equal to (5.0 + 0.3) x 10^4 sec^{-1} at 22°C, has been also determined. In addition, fragmentation of radical $C_6H_5CH_2CH_2\dot{C}HCF_3$ has been first found in this example by ESR technique; i.e. the third process - fragmentation - is added to the two competing processes, in which this radical participates : (1) the chain transfer and (2) the addition to monomers. The fragmentation causes certain corrections in kinetic parameters of the process (ref. 23), as we shall see below.

$$C_6H_5CH_2CH_2\dot{C}HCF_3 \xrightarrow{K_{fr}} C_6H_5\dot{C}H_2 + CH_2=CHCF_3$$

The following studies showed that the same process was registered (by ESR technique) for radical $C_6H_5CH_2CH_2\dot{C}H_2$ (reaction of benzyl bromide with ethylene). The fragmentation was not observed for radicals $C_6H_5CH_2CH_2\dot{C}HCl$ and $C_6H_5CH_2CH_2\dot{C}HSiMe_3$ (under the comparable conditions) in the reactions with vinyl chloride and vinyltrimethylsilane.

The relative constants of addition (K_{ad}) of radical $C_6H_5\dot{C}H_2$ were estimated for the unsaturated compounds listed in Table 2 under metal complex initiation by method of competing kinetics; the addition of benzyl radical to vinyltrimethylsilane was taken as standard (K_{ad}^{Si}) (ref. 24).

Table 2 : The relative constants of addition

X in CH_2=CHX	K_{ad}^X / K_{ad}^{Si}
C_4H_9	0.29 ± 0.04
CF_3	0.22 ± 0.08
$SiMe_3$	≡ 1
Cl	1.02 ± 0.14
CO_2CH_3	11.9 ± 1.7
CN	24 ± 5.1

We can see from these data that benzyl radical significantly easier adds to electrophilic methyl acrylate and acrylonitrile than to relatively nucleophilic hex-1-ene. This is one of the arguments for a nucleophilic character of benzyl radical. The polar factors affect essentially kinetic parameters of the processes, as judged from the ratios $K_{ad}CN / K_{ad}C_4H_9 = 83$ and $K_{ad}COOCH_3 / K_{ad}C_4H_9 = 41$. The $K_{ad}COOC_2H_5 / K_{ad}Me = 46$ (i.e. is of the same order with that obtained for $C_6H_5\dot{C}H_2$) was found in kinetic studies of addition of the knowingly nucleophilic cyclohexyl radical to monomers $CH_2=CXC_6H_5$ (ref. 25), in which the determining influence of polar factor on addition rate is stated. The unexpected result - the ratio $K_{ad}CF_3 / K_{ad}SiMe_3$ is close to that for hex-1-ene, not for methyl acrylate - causes an interest in studying the data obtained (ref. 23). One of possible explanation of this fact is the mentioned above fragmentation of the radical-adduct, which finally leads to abnormal decrease in adduct content (whose concentration is used in the calculations) in the reaction mixture. We can also note the same for the reaction of $C_6H_5CH_2Br$ with vinyl chloride ($K_{ad}Cl / K_{ad}SiMe_3 \approx 1$). Although the fragmentation of $C_6H_5CH_2CH_2\dot{C}HCl$ radical was not found in ESR studies, this can play a definite role under the conditions of the reaction (140°C). This is more probable, because the calculations of the activation energy of the addition of $C_6H_5\dot{C}H_2$ radical to vinyl chloride resulted in the essentially lower value (by 7 Kcal/mol) than that for the reaction with vinyltrimethylsilane; i.e. there is no anomalies at the step of addition : this step is more profitable energetically vinyl chloride than in the case of vinyltrimethylsilane (ref. 20).

The reaction of benzyl bromide with vinyltrimethylsilane was used for studying a general kinetics of addition under conditions of metal complex initiation (ref. 26). One of the crucial questions in this case is how the chain transfer step proceeds : by "purely" homolytic mechanism (*via* benzyl bromide) :

$$C_6H_5CH_2(CH_2CHX)^{\bullet}_n + C_6H_5CH_2Br \longrightarrow$$

$$\longrightarrow C_6H_5CH_2(CH_2CHX)_nBr + C_6H_5\dot{C}CH_2$$

or, alternatively by the redox catalysis mechanism

$$C_6H_5CH_2(CH_2CHX)^{\bullet}_n + [Fe(CO)_nL_{5-n}Br] \longrightarrow$$

$$\longrightarrow C_6H_5CH_2(CH_2CHX)_n\,Br + [Fe(CO)_nL_{5-n}]$$

It is natural that a general kinetic equation for every case is different :

(a) for radical process, as follows :

$$V(T_1Br) = K_{rad} [FeL]_o^{1/2} [S]_o^{1/2} [M]_o,$$

where S is benzyl bromide; M - monomer; L - ligand; T_1Br is the adduct; K is the combination of constants;

(b) for the redox process :

$$V(T_1Br) = K_{redox} = [FeL]_o[S]_o$$

Studying the reaction orders for every reagent and initiating system $Fe(CO)_5$ + DMF (1:3) showed that in this specific reaction the radical mechanism of a chain transfer was more probable. However, in other reactions a mechanism can change depending on the reagents nature and their capability of forming more or less stable complexes with $Fe(CO)_5$.

When we investigated the competing kinetics in the reaction of $C_6H_5CH_2Br$ with acrylonitrile and vinyltrimethylsilane modelling the cotelomerization processes of one telogene with two monomers (ref. 27), we paid our attention to the interesting specific feature of this reaction, which consisted in the rare phenomenon of the almost full atlernation - regular alternating monomers in the telomer molecule - with determining influence of polar factor. In this case the only cotelomer $C_6H_5CH_2CH_2CH(CN)CH_2CHBrSiMe_3$ of the possible ones is formed; the nucleophilic benzyl radical adds effectively to acrylonitrile, and the formed electrophilic radical $C_6H_5CH_2CH_2\dot{C}HCN$ adds only to relatively nucleophilic vinyltrimethylsilane.

REACTIONS OF ORGANOBROMINE COMPOUNDS CONTAINING OTHER HETEROATOMS

Proceeding the reaction of bromocyane with 1,1,1-propellane differ essentially from that for CCl_3Br (ref. 14). In the case of bromocyane telomers CN-( )$_n$-Br are formed (Table 1), but the main products are the second (n = 2) and the third (n = 3) telomers in a 4:1 ratio, such a distribution of telomers is unusual for

telomerization. In addition, bromocyane also plays the role of brominating agent in this reaction : the corresponding dibromide was found in the reaction products.

The photoinitiated reaction of 1,2-dibromo-1-chlorotrifluoroethane with chlorotrifluoroethylene gives the first two telomers (ref. 28).

$$BrCClFCF_2Br + CClF{=}CF_2 \xrightarrow{UV} Br(CF_2CClF)_n(CClFCF_2)_mBr$$
$$(n = 1, m = 1, 2)$$

The general telomer formula, the authors presented means the possibility of participating of several molecules of both monomer and telogen, although the corresponding compounds are not identified. Under radiation or heating N-bromodifluoromethyleneimine easily reacts with fluoroolefines $CF_2{=}CFX$ (X = F, Br) to afford adducts $CF_2{=}NCF_2CFXBr$ in good yields (X = F, yield = 82 %; X = Br, yield = 67 %) (ref. 29).

CHARGE TRANSFER COMPLEXES AS INTERMEDIATE IN RADICAL PROCESSES

As is seen from the previous chapters, the complex system based on $Fe(CO)_5$ combined with nucleophilic co-initiator (DMF, HMPA) are high efficient initiators of radical processes of polybromoorganic compounds. A great available qualitative research results show the occurrence of correlation between the efficiency of a system as initiator and the nature of reagents and polar character of intermediate radicals. IR spectra were fairly successfully attempted to be used for studying the character of intermediate particles, search for any quantitative parameters determining the efficiency of a system. The authors (refs. 30, 31) have managed to show that charge transfer complexes (CTC) are formed in a number of reactions involving organobromine compounds; the quantitative characteristics of the charge transfer bond (intensity and shift of the bond position in spectrum in comparison with its position for initial system) are correlated with efficiency of the given metal complex system as an initiator of reaction. The body of the data obtained for systems with step-by-step adding reagents allows us to assume that the initial step of the reactions of organobromine compounds with functionally substituted monomers is forming complicated CTC involving all the reacting components. At the same time, the investigations of the CTC of the simpler systems - double, triple, and, finally, four-membered (all components of the reactions : $Fe(CO)_5$, DMF, CBr_nH_{4-}

$_n$, CH_2=CHX) allows us to present correctly the initiating activity of competing system and its prospects for initiating the precisely given combination of interacting reagents. This can essentially facilitate the choice of initiating systems with no complicated chemical experiments in practice. The similar research was conducted later using carbonyls of manganese, chromium, molybdenum, wolframs (ref. 32). These series also demonstrated the satisfactory qualitative correlations between characteristics of CTC and efficiency of initiation of homolytic addition and telomerization, proceeding with C-Br bond repture.

THE USE OF ^{13}C NMR SPECTRA IN SOLVING THE STRUCTURE OF ORGANOBROMINE COMPOUNDS

Researchers consider as one of important problems, the use of such physical methods of studying the structure of organobromine compounds, which could solve the structure of new compounds not only by comparison of spectra parameters with those obtained for the standard compounds, but allow us to calculate these parameters for various possible structures beforehand. In this respect, NMR spectroscopy is the most promising method. For years of studying organobromine compounds many experimental results were obtained (ref. 33) which allowed the authors to find certain quantitative relationships of changes in character of signals referred to organobromine groups depending on a number of bromine atoms and degree of substitution of the neighboring carbon atoms. In addition the fairly detailed topological scheme (possessing a certain predictable potential) for empirical estimation of chemical shifts of ^{13}C NMR in polybromoalkanes was developed on the basis of the data mentioned above. In these works the authors attempted to find an equation connecting the topological image of molecule with experimental values of ^{13}C in polybromoalkanes, taking into account that interaction can be occur both *via* space and throughout the chain (refs. 34, 35).

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BROMIDES IN ZEOLITE SYNTHESIS / ZEOLITES IN BROMIDE SYNTHESIS AND CONVERSION

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ABSTRACT

Quaternary ammonium bromides and hydroxides (quats) are applied as templates in the synthesis of zeolites with relatively high Si/Al ratio. Examples will be given of the use of mon-, di-, poly- and associated quats as templates in zeolite growth. Templated zeolites of the MFI-type can be grown in a lateral or in an axial way onto metal supports, providing promising composite systems, for separation and catalysis, respectively.

Upon calcination the template is removed and the zeolite's well-defined pores are available for adsorption and catalysis. Particularly challenging is the field of electrophilic aromatic substitution. Here often non-regenerable metal chlorides serve as the catalyst in present industrial practice. Zeolites are about to take over the job and in fact are doing so for aromatic alkylation.

Aromatic brominations have been mainly carried out using X, Y and L zeolites. Improved para/ortho ratios have been observed upon brominating halobenzenes, benzyl halides, and biphenyl. The side product HBr leads to decreased activity and selectivity. This problem has been addressed by adding scavengers, by working in the gas phase, and by applying oxidative bromination.

Silver(I)-loaded zeolites and silica-alumina can be used in carbohydrate coupling. The Ag(I) activates the 1-Br-substituent in this nucleophilic substitution. Because of the size of the reactants only the outer surface of the zeolites is active.

Cu-exchanged zeolites have been examined in the nucleophilic substitution of halobenzenes towards aminated and oxygenated systems. Selectivities are dependent on the zeolite's pore sizes.

Upon passing bromobenzene and hydrogen over zeolite Pt-H-beta dehydrobromination followed by hydrogenation and isomerization takes place. In this way undesired aromatic bromides can be recycled.

INTRODUCTION

Quaternary ammonium compounds (quats) are prepared - by moderate heating of the amine and the alkyl halide in a suitable solvent - as the chlorides or the bromides. Subsequently conversion to the hydroxides may be carried out. Major applications of the quat chlorides are as fabric softeners and as starch cationizing agent. Several bio-active compounds (agrochemicals, pharmaceuticals) possess the quat-structure. Important applications of quat bromides are in phase transfer catalysis and in zeolite synthesis.

Zeolites have the following characteristics: (ref. 1) they are crystalline aluminosilicates (tetrahedral connection) with accessibility ranging from .3-.8 nm. All atoms are exposed to the pore system which can consist of parallel channels (1-D) or of a threedimensional system (3-D). Some common zeolites with their accessibility and minimum Si/Al ratios are given in Table 1.

Table 1. Some common zeolites.

Code[a]	Oxygen rings window or channel[b]	Access. nm	Dim.	Si/Al
A (LTA)	8	.4,5	3-D	1
X, Y (FAU)	12	.80	3-D	≥ 1
L (LTL)	12	.70	1-D	≥ 3
MORD. (MOR)	12	.70	1-D	≥ 5
BETA (BEA)	12	.75	3-D	≥ 5
ZSM-5 (MFI)	10	.57	3-D	≥ 10

a Between brackets the official 3-letter code.

b Oxygen is larger than Si, Al. Oxygen sub-lattice governs the accessibility.

It may be noted that the ion exchange capacity is directly connected with the Al-content (each Al provides one negative charge). The zeolite used in detergent formulations (over 10^6 t/a) is NaA with Si/Al = 1, so with maximum exchange abi'ity.

Zeolite crystals can be grown in sizes ranging from 0.5 μm to several hundreds μm and often have a characteristic morphology. Thus type A zeolites are cubes,

type X and Y octahedra, type L cylinders and type MFI prismatic elongated or more cube-like crystals.

Quaternary ammonium compounds as structure directing agents in zeolite synthesis

In zeolite synthesis (ref. 2) an aqueous mixture containing a silicon source, an aluminum source, an alkali source (usually NaOH) is autoclaved and subjected to hydrothermal treatment. Hydrated Na-ions are then filling the pore system in the as-synthesized zeolite. In the case of relatively high Si/Al zeolites an organic template is required which is usually a tetraalkylammonium compound, applied as the bromide or the hydroxide.

Thus in the synthesis of BEA and MFI, tetraethyl- and tetrapropylammonium ions respectively, are most frequently applied as the templates.

In the as-synthesized MFI-crystals the tetrapropylammonium (TPA) ions are occupying the intersections between the straight (parallel) and the sinusoidal channels of the zeolite, thus providing an efficient pore filling. The detailed structure of as-synthesized MFI-TPA has been elucidated by X-ray single crystal analysis (ref. 3). Also the combination tetrabutyl-/tetraethylammonium can be applied as template in MFI-synthesis. A 1:1 build-in is found then (Fig. 1). When only tetrabutylammonium is available as template, the MEL (ZSM-11) lattice is formed with another distance between the channel intersections.

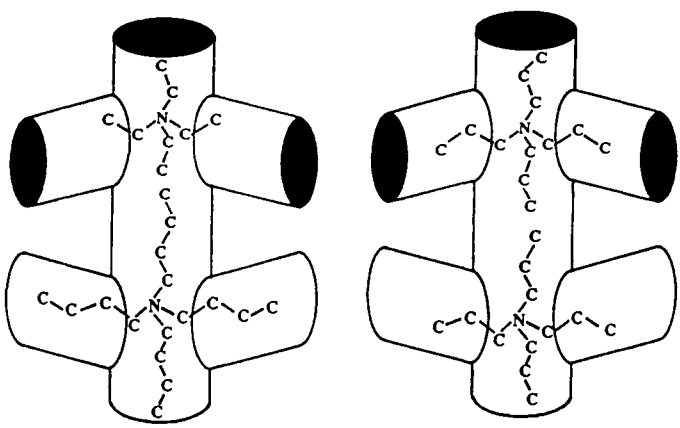


Figure 1. Structure-directing quats in the MFI-lattice : right, the usually applied tetrapropyl-ammonium, left, tetrabutyl- and tetraehtylammonium 1 :1.

In our group we have also studied some diquat systems of the type $(propyl)_3N(CH_2)_xN(propyl)_3$. Molecular mechanics calculations (ref. 4) showed the following order of stability of the zeolite including the template:
$x = 5 < x = 6 < x = 7 <$ TPA (2 x) (Table 2).
Furthermore it became clear from the calculations that the diquats will prefer the straight channels of the MFI crystals (Fig. 2). The observed enhanced crystal growth in the b-direction (ref. 4) may be taken as a confirmation of this.

Table 2. Relative energies of the zeolite MFI-framework (4 al/u.c.) Including the template.

Template	Rel. Energy kJ/mol u.c.
$Pr_3N(CH_2)_5NPr_3$	62.0
$Pr_3N(CH_2)_6NPr_3$	18.4
$Pr_3N(CH_2)_7NPr_3$	10.5
TPA	0.0
1,4-Pr_3N Cyclohex NPr_3	36.0

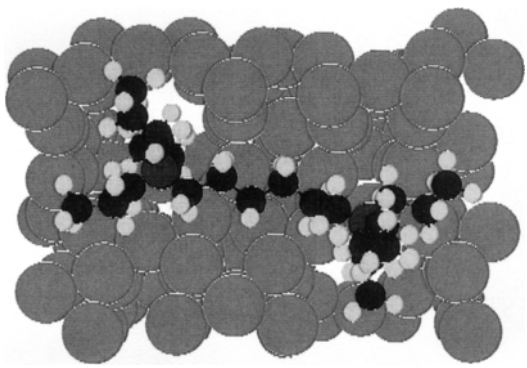


Figure 2. View of the location of the biquat hexapropyl-1,6-hexanediammonium in a straight channel of the MFI-framework.

The importance of quats as structure-directing agents in zeolite synthesis was recently underlined (ref. 5) by the synthesis of the new zeolites SSZ-26 and -33, which combine 10- and 12-ring pores. The templates applied are shown in Figure 3.

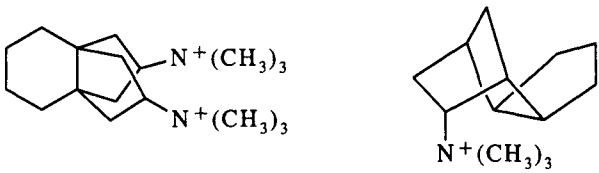


Figure 3. Templates used in SSZ-26 (left) and SSZ-33 synthesis.

A tetracyclic triquat system has been applied (ref. 6) in the synthesis of ZSM-18, the first known zeolite to contain rings of three (Si, Al)-O species (3-rings). The structure of ZSM-18 consists of parallel 12-ring channels equipped with side pockets.

Finally, we mention the use of the polyquat bromide "Dab-4-Br" - easily prepared from Dabco and 1,4-dibromobutane - in the synthesis (ref. 7) of gmelinite (a 1-D 12-ring zeolite).

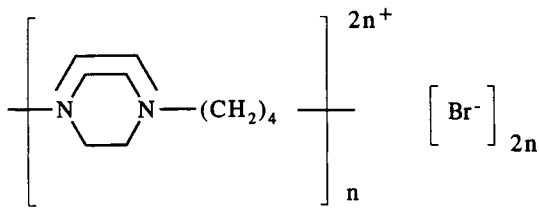


Figure 4. Polymeric quat Dab-4-Br applied in the synthesis of gmelinite

An interesting aspect here is the length of the crystal - in the direction of the parallel channels - in relation to the polymer length. A polymer molecular mass of 10.000 corresponds with a length of 0.05 μm. So some 20 polymer chains are required for a crystal length of 1 μm.

In the above work quats are occluded in zeolite lattices in a molecular way. In the recently disclosed (ref. 8) superwide pore M41S-materials quats arranged in the

form of cylindrical micelles serve as templates. Thus the zeolitic material MCM-41 - a member of this family - is prepared using cetyltrimethylammonium as template. Concentration and temperature are chosen such that this long chain quat forms cylindrical micelles which arrange together in a hexagonal array (Figure 5). The silica(te) is assumed to crystallize around and between the micelles.

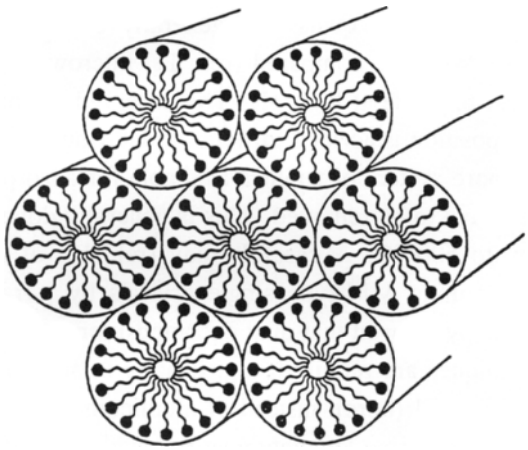


Figure 5. Hexagonal array of cylindrical micelles of cetyltrimethylammonium in MCM-41 synthesis

MCM-41 can be synthesized with Si/Al ratio ≥ 15. After calcination the pore diameter was determined by adsorption techniques and by thermoporometry (ref. 9) to amount to 4.0 nm.

Our group has recently observed (ref. 10) that often synthesis time of zeolites can be substantially shortened when microwave radiation is applied instead of conventional heating. Table 3 gives some examples. Also a narrow crystal size distribution is obtained in this way. The crystallization temperature is rapidly (1 min) reached by microwave heating, this may be a factor in homogeneous and essentially simultaneous nucleation.

Table 3. Reduced synthesis times by applying microwave heating.

	Conventional	Microwave
NaA	2 hr	10 min.
NaY	10 hr	10 min.
ZSM-5	> 48 hr	30 min.

The Hofmann degradation of quats will generally constitute a side reaction during zeolite synthesis. We have compared (ref. 11) microwave and conventional heating of aqueous TPA bromide at high pH. The observed strong effect of ageing on the Hofmann decomposition is acribed to water structuring.

In order to get the pore system of zeolites available for adsorption and catalysis the template molecules have to be removed. This is generally done by calcination in air at temperatures up to 500 °C. A careful study (ref. 12) of the calcination of as-synthesized TPA-containing MFI-type single crystals by infrared spectroscopy and visible light microscopy showed that quat decomposition sets in around 350 °C. Sometimes special techniques are required, e.g. heating in an ammonia atmosphere (ref. 13) in the case of B-MFI (boron instead of aluminum present) to prevent loss of crystallinity of the zeolite during template quat removal.

Controlled removal of the template is especially important when zeolite based membranes are involved consisting of a continuous MFI layer on a ceramic or sintered metal support (ref. 14). In these novel composite ceramic membranes the formation of cracks during template removal would be detrimental. The unique properties (ref. 14) of metal-supported MFI-layer membranes prove that indeed crack formation can be essentially prevented.

Besides lateral (parallel) growth of MFI layers onto a porous metal support, also axial growth of MFI crystals onto (dense) metal supports is possible leading to interesting new composite catalysts.

Thus zeolite ZSM-5 can be grown (ref. 15) onto a stainless steel metal gauze as shown in Figure 6. Presumably the zeolite crystals are chemically bonded to the (chromium-) oxide surface layer of the gauze. After template removal by calcination and ion exchange with Cu(II) a structured catalyst is obtained with excellent performance (ref. 15) in $DeNO_X$ reactions using ammonia as the reductant.

The system survives the calcination and the thermal reaction cycles without any damage.

Figure 6. SEM picture of ZSM-5 crystals grown onto a stainless steel wire gauze. The wire diameter is 35 μm.

Zeolites as catalysts and promoters in organic bromide synthesis and conversion

In the second part of this contribution the use of zeolites in the synthesis and conversion of organic bromides will be discussed (ref. 16).

Aromatic bromination

In general the field of aromatic substitution constitutes the challenge to the organic chemist to develop clean technologies. In the present industrial practice often non-regenerable metal chlorides or mineral acids serve as the catalysts.

Zeoliltes seem particularly suited to take over the job and in fact are doing so already for aromatic alkylation. Thus in ethylbenzene manufacture (from benzene and ethene) modern processes apply zeolites (H-ZSM-5, H-Y) as the catalyst, substituting conventional processes based on $AlCl_3$ or BF_3-on-alumina catalysis. Substantial waste reductions are achieved.

For cumene production (from benzene and propene) a new process has been developed in which H-mordenite (with high Si/Al) serves as the catalyst. Here the

present-day catalyst is a special supported phosphoric acid system which cannot be regenerated.

Much research is devoted nowadays to zeolite-catalyzed acylation (ref. 17) and nitration (ref. 18). In both fields promising results have been obtained.

Quite some papers and patents deal with zeolite-catalyzed aromatic bromination. Most work pertains to bromination of halobenzenes and of toluene, using X-, Y- and L-type zeolites.

In an early paper by our group (ref. 19) halobenzenes are brominated at 298 K in the liquid phase over various Y-zeolites (Fig. 7). Improved p/o-ratios with respect to conventional ($FeBr_3$) catalysis are observed.

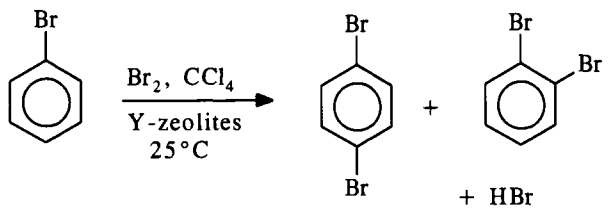


Figure 7. Zeolite-catalyzed bromination of bromobenzene.

Several variables were studied such as the counter cation(s) in the zeolite, the activation temperature, the solvent and the effect of additives.

Multivalent cations (Ca(II), Ce(III)) showed a higher activity than monovalent cations (Na, K). In toluene bromination (ref. 20) the catalytic activity of multivalent cations embedded in a zeolite matrix appeared to be higher than that of the corresponding metal chlorides.

From adsorption isotherms and competitive adsorption experiments (ref. 19) the strength of adsorption of the reaction components on zeolite CaY appeared to be HBr > o-dibromo > bromo- > p-dibromobenzene > Br_2.

When applying zeolites with relatively low Si/Al ratio such as Y the hydrogen bromide formed in the reaction is a problem because of its strong adsorption accompanied by gradual loss of crystallinity of the zeolite. This problem has been addressed in several ways.

De la Vega and Sasson (ref. 20) added propene oxide as a HBr-scavenger in the bromination of toluene over NaY in CCl_4 and obtained an initial p/o-ratio

selectivity of 98/2 compared to 80/20 as the highest reported value. A disadvantage was catalyst deactivation, presumably due to propene oxide polymerization.
Our group suppressed (ref. 19) the deactivation by HBr by the addition of $NaHCO_3$ as a scavenger for HBr and zeolite KA for removal of water formed in the latter reaction. With these additives a p/o-selectivity of 97/3 was achieved in the bromination of bromobenzene over CeY.

A third approach is to apply gas phase bromination. Thus fluorobenzene has been brominated with high p-selectivity over MgY (ref. 22) or with HBr/O_2 over CuY (ref. 23).

A fourth option is to apply high silica zeolites (de-aluminated mordenite, US-Y or beta) to cope with the HBr formed.

The order in reactivity in the Y-zeolite catalyzed bromination found is:
toluene > benzene > fluorobenzene > chlorobenzene > bromobenzene

This result together with the preferred formation of para-products suggests that the attacking species is electrophilic and that consecutively are involved: formation of a charge transfer complex, addition of Br^+, and elimination of H^+. This picture is supported by Raman studies (ref. 24) of the system Br_2-benzene-NaX.

The important question how inner and outer surface of the zeolite crystals contribute in the aromatic bromination has been discussed by Sasson et al. (20).
Zeolite CaY was recently applied in the bromination (CH_2Cl_2, 20 °C) of benzyl bromide (ref. 25). Selectivity to the 4-bromo derivative was 79% at a conversion of 76%.

The same group also subjected biphenyl to zeolite-catalyzed bromination. Applying a solventless process (100 °C) and zeolite NaKL as the catalyst the desired 4,4'-dibromo compound (Fig. 8) was obtained in a selectivity of 75% at 100% conversion (17% of 4-mono-Br).

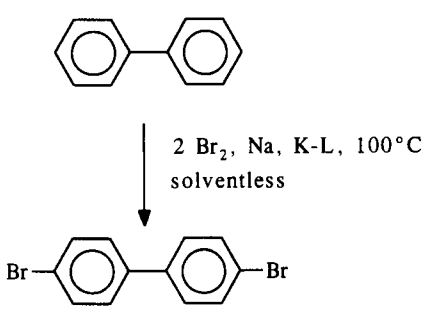
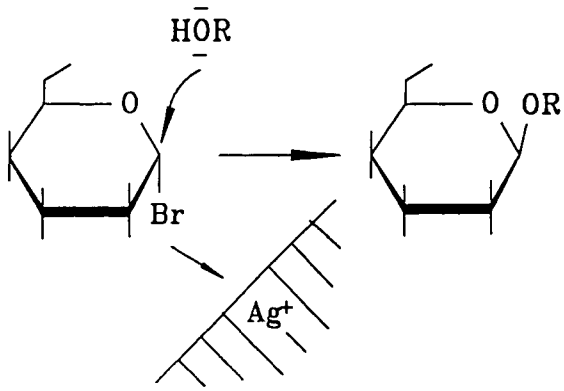


Figure 8. Bromination of biphenyl.

Finally we mention in this section the non-catalytic selective bromination of aniline by the application of a zeolite pre-loaded with Br_2 as a slow release reagent (ref. 27). Aniline, dissolved in CCl_4 was treated with Br_2 adsorbed onto various zeolites and zeolite CaA was found to be most selective for monosubstitution (92%). The addition of organic bases improved the performance, probably due to scavenging of HBr. Also the toluidines could be monobrominated with this system with > 95% selectivity.

Carbohydrate-coupling

Carbohydrate-coupling or glycosylation, is a major synthesis method in carbohydrate preparation. Silver silicates and Ag(I)-exchanged zeolite A - so-called insoluble Ag(I) - have been advocated as promoting agents, applied in more than stoichiometric amount (Fig. 9). All hydroxyl groups except the attacking one are suitably protected.



Ag^I zeolites in carbohydrate coupling

Figure 9. Ag-zeolite promoted glycosylation.

The stereoselectivity is an important issue here: an S_N2 reaction would lead to inversion at C_1, a two-step reaction, with first formation of an adsorbed

oxocarbenium ion on the surface followed by attack by the HO-reactant from the liquid phase would do the same.

In view of the accessibility of zeolite A (only linear molecules adsorb) the coupling will take place at the outer surface of the zeolite crystals. Indeed, Ag-Y and especially a Ag-loaded amorphous silica-alumina, containing a spectrum of wider pores, turned out to be much better promoter-agents (ref. 28). The silica-alumina is etched with aqueous NaOH and subsequently exchanged with Ag(I).

The Ag-silica-alumina material is furthermore suited to assist in sterically hindered aromatic brominations. As an example we converted 1,3,5-tri-t-butylbenzene into 2,4,6-tri-t-butylbromobenzene. When using an acidic zeolite and Br_2 de-alkylation prevails and 3,5-di-t-butylbromobenzene is formed (ref. 29).

Nucleophilic substitution of halobenzenes

Various Cu-exchanged zeolites have been examined in the nucleophilic substitution of bromo- and chlorobenzene towards aminated and oxygenated compounds (ref. 30). In amination a consecutive reaction to diphenylamine and reduction to benzene are the side-reactions (Fig. 10).

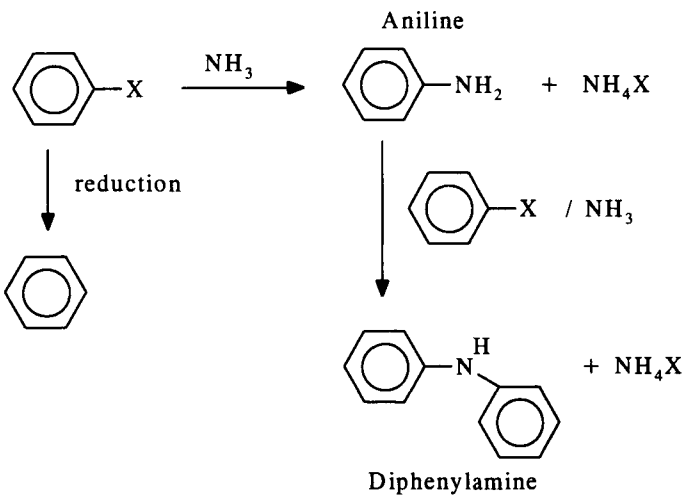


Figure 10. Reactions in Cu-zeolite catalyzed amination of halobenzenes.

The selectivity of the gas phase amination is highly dependent on the type of zeolite as shown in Figure 11 for five zeolites all containing 3 wt % of Cu. When the zeolite becomes more spacious (L, Beta) the consecutive reaction increases which is understandable. Over Cu-Y reduction predominates.

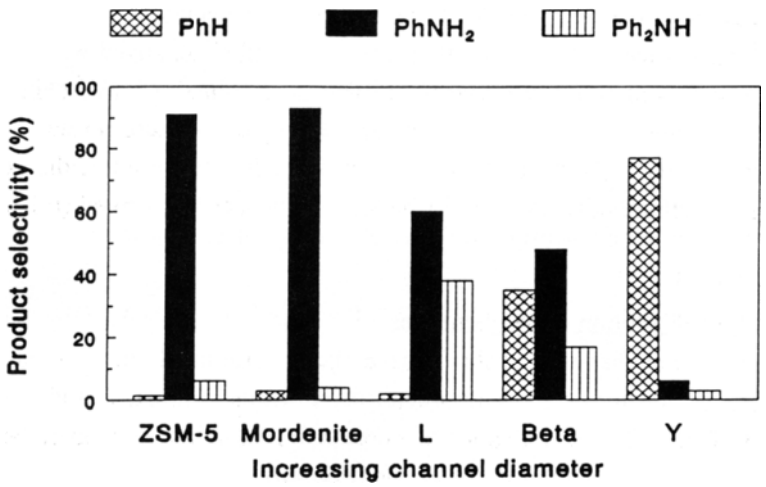


Figure 11. Selectivities in Cu-zeolite catalyzed amination (400°C, 3 h on stream).

We observed that the reduction side-reaction can be suppressed substantially by applying CO_2 as the carrier gas (ref. 31). Perhaps the adduct of CO_2 and NH_3 acts as a Cu(I) ligand and protects the Cu(I) for reduction towards Cu(O). Recently a similar CO_2 promoting effect was reported (ref. 32) for the liquid phase conversion of aromatic bromides towards methoxyarenes.

Hydrodebromination of aromatic bromides

Finally we mention that aromatic bromides can be debrominated by hydrogen and a metal(o)-in-zeoite system (ref. 33). Over e.g. Cu(O)-Y bromobenzene is converted into benzene whereas over Pt-H-beta (200 °C) quantitative hydrodebromination is followed by hydrogenation and isomerization towards methylcyclopentane (Fig. 12). In this way undesired aromatic bromides can be recycled.

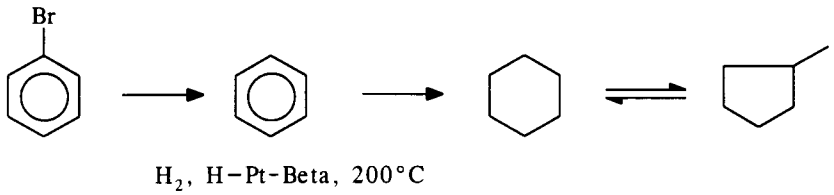


Figure 12. Combined hydrodebromination-hydrogenation-isomerization of bromobenzene.

SOME CONCLUSIONS

- Quaternary ammonium bromides play an important role in the synthesis of high silica zeolites
- New developments in these type of zeolites include composite systems and super large pore systems
- Zeolites serve as catalysts
  - in preparing Br-containing target molecules
  - in converting intermediate Br-compounds
  - in recycle of organic bromides

ACKNOWLEDGEMENTS

The author is much indebted to the following people who were engaged with the work presented: A. Arafat, M.H.W. Burgers, E.J. Creyghton, E.R. Geus, B. van de Graaf, A.J. Hoefnagel, J.C. Jansen, G.J. Klap, M.A. van Koten, C.H. Legein, R. de Ruiter, E. de Vos Burchart and Th.M. Wortel.
Thanks are due to Dr. J. Dakka for fruitful discussions.

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AN IMPROVED SYNTHESIS OF BIARYL DERIVATIVES VIA THE PALLADIUM CATALYZED COUPLING OF ARYL BROMIDES

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ABSTRACT

Functional biaryl derivatives are important industrial chemicals. They are used as monomers for the production of high performance and other polymers, as well as dyes, pharmaceuticals and agrochemical intermediates. We have developed an improved method for the dehalogeno-dimerization of aryl bromides to yield biaryl derivatives under mild conditions (temperature : < 100°C, atmospheric pressure) using a common base, a 5 % Pd/C catalyst (0.1 - 10 % w/w, based on the starting material) in an aqueous medium and formyl hydrazine as the reducing agent. Several examples of biaryl derivatives are discussed.

INTRODUCTION

Biaryl derivatives bearing reactive groups have become increasingly important in industry. Uses for this class of compounds are constantly being developed in the production of high performance polymers. Materials such as 3,3',4,4'-biphenyl-tetracarboxylic dianhydride **1** and 4,4'-biphenol **2** are monomers employed in the manufacture of high performance polyimides or polyesters. Applications for this family of molecules have also been found both in the dye industry and in the pharmaceutical industry.

In the presence of a precious metal catalyst, aryl halides can undergo dehalo-dimerization to give biaryl products, with varying degrees of selectivity. The major byproduct of this reaction is usually the dehalogenated aryl compound. This type of chemistry is currently one of the very few viable means for the large scale preparation of biaryl compounds.

The reaction outcome is critically dependent on the nature of the reducing agent. The function of this reagent is described in the following equations

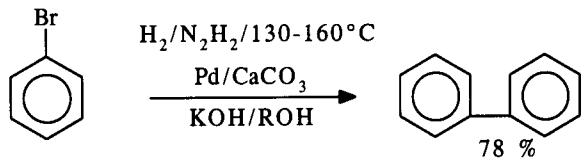
$$2\ ArBr + Pd\ [0] \rightarrow Ar\text{-}Ar + PdBr_2 \quad (1)$$

$$PdBr_2 + \{Reducing\ Agent\} \rightarrow Pd\ [0] + HBr \quad (2)$$

$$HBr + MOH \rightarrow MBr + H_2O \quad (3)$$

The range of chemicals capable of reducing Pd to the zero oxidation state is vey wide; however it is remarkable that the desired selectivity towards the coupling pathway depends in a large measure on the choice of reducing agent.

Busch and Weber (ref. 1) first reported the Pd catalyzed coupling of halogenated aromatic compounds. Their reaction conditions and some examples of their work are shown in equations (4) to (7).



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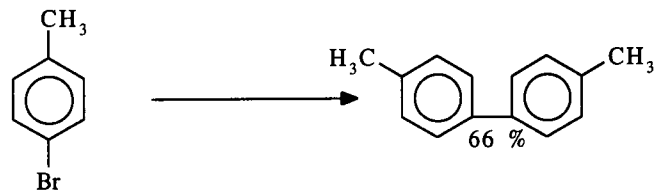

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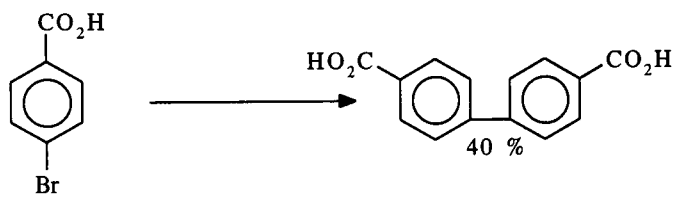

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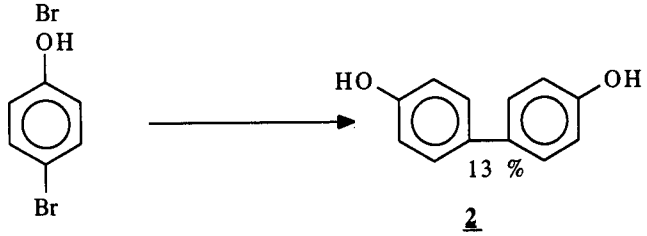


(7)

2

The contemporary patent literature contains numerous examples of reducing agents for this synthetic methodology. A selection of such reagents is shown in Table 1; this particular sampling relates to industrial methods for the coupling of halogenated phthalic acids, to give 3,3',4,4'-biphenyltetracarboxylic acid **3**, a precursor of **1**.

Table 1. Patent literature reducting agents for the synthesis of 3

Reducing agent	Coupling yield	Temperature	Reference
Glycerol	53-64 %	150°C under pressure	2
Chloroform/Methylamine	74 %	126°C under pressure	3
Glycerine / H_2	64 %	150°C under pressure	4
Ethylene Glycol	28-42 %	aq. medium, reflux	5
Methanol	37 %	aq. medium, reflux	5
Paraformaldehyde	38 %	aq. medium, reflux	5

The methods reported in these and other patents are plagued by low yields; furthermore they normally necessitate the use of high pressure technology. The expensive precious metal catalyst must be recovered and reused. In most cases, selectivity and reaction rates deteriorate when recycled catalyst is used. No reports of adequate recovery of catalyst activity have been found.

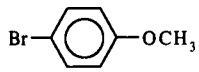
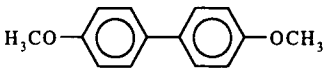
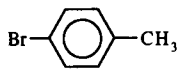
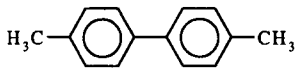
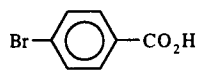
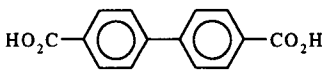
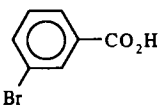
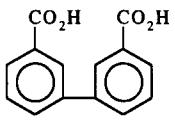
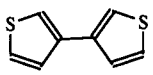
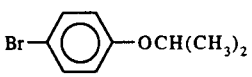
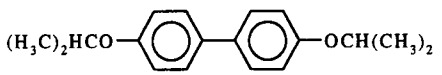
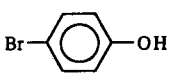
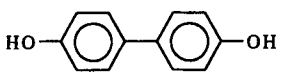
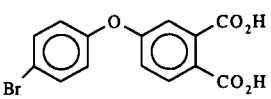
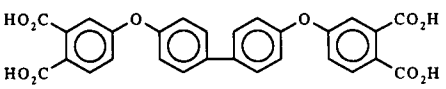
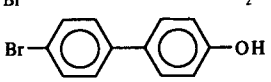
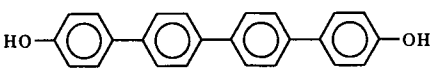
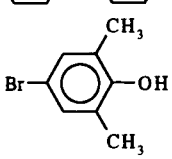
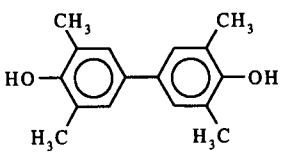
Other recently disclosed processes mention the use of reducing agents such as sodium formate (ref. 6), combinations of sodium formate with various formate esters or amides (ref. 7) and hydroxylamine sulphate (ref. 8). These materials are reported to give acceptable yields, still they require large amounts of either catalyst or reducing agent or of both. There is also a marked difference in the performance of these agents when applied to substrates containing different functional groups; in some cases almost no coupling takes place and instead dehalogenation is the dominant reaction.

RESULTS AND DISCUSSION

Recently we found that formyl hydrazine **4** is an excellent reducing agent for haloaryl couplings. This compound gives high coupling selectivities and reaction rates with a wide range of haloaromatic substrates. The reaction is carried out in water, regardless of the solubility of the substrate.

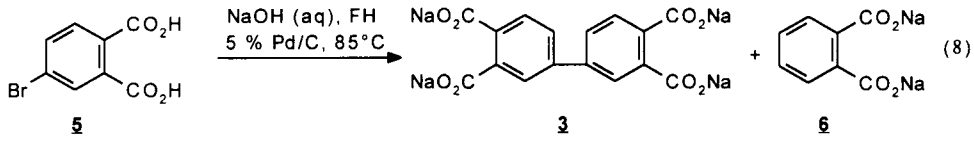
Table 2 shows some examples of the scope of this reagent :

Table 2. The scope of formyl hydrazine promoted bromoaryl dimerization

Substrate	5 % Pd/C to substrate ratio (% w/w)	Product (*)	Coupling %
	5		87 (**)
	6		75 (**)
	5		64 (***)
	5		88 (***)
	6		67 (**)
	5		78 (**)
	10		95 (***)
	0.6		93 (***)
	0.8		86 (***)
	5		86 (***)

Notes : * : Substrate conversion : 100 % in all examples; ** : GC area %; *** : HPLC area%.

The development of an advantageous large scale synthesis of **3** starting from 4-bromophtalic acid **5** was based on the formyl hydrazine method (Eqn. 8). In the course of this work we made some interesting observations on the conditions under which **4** operates.



5 **3** **6**

The dimerization process was carried out in a basic aqueous medium, below reflux temperatures. Usually the reaction was complete in less than one hour.

We compared a variety of reducing agents and found that in most cases the reaction did not go to completion (see Table 3). In those instances in which all the starting material was consumed, the coupling performance was poorer than that obtained with **4**. Interestingly, formaldehyde showed two distinct modes of action. When pretreated with bases it promoted coupling, whereas by itself (in the presence of base but without pretreatment) its activity was reversed leading mostly to reduction.

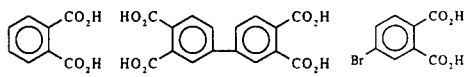
Table 3. Influence of reducing agents
Conditions : Pd/C 5 %, aq. NaOH, 85°C

Reagent	Time (h)	**6** (a)	**3** (a)	**5** (a)
CH_2O + NaOH	1	16	82	
CH_2O + $N(CH_3)_3$	1	23	72	
CH_2O	> 1	75	18	
Sugar	> 1	12	17	59
Isopropanol	> 1	5	0.4	79
Ethylene Glycol	> 1	22	57	11
Propylene Glycol	> 1	10	8	46
$NaHCO_2$	> 1	30	70	
Formylhydrazine	0.5	10	90	

a) HPLC area %; balance% : unidentified impurities.

Does **4** act by first undergoing hydrolysis into its components ? We performed a series of experiments directed at answering this question. We found that in the presence of either hydrazine or formate, there was a drop in reaction kinetics and selectivity (see Table 4).

Table 4. Effect of reducing agent structure on reaction pathway

Catalyst to Substrate ratio (% w/w)	Reducing Agent	Reducing Agent to substrate ratio (mole equiv.)	Time (hours)	HPLC Area % 		
				6	**3**	**5**
0.2	**4**	0.33	0.5	10	90	
0.2	**4**	0.33	0.5	9	79	12
	HCO_2Na	0.33				
0.2	**4**	0.33	0.5	10	86	5
	Hydrazine	0.19				
0.2	**4**	0.33	0.5	12	83	5
	Hydrazine	0.16				
	HCO_2Na	0.16				
0.2	Hydrazine	0.33	0.5	25	75	
	HCO_2Na	0.33				
0.2	Hydrazine	0.33	0.5	43	7	50
0.2	Oxalyl Dihydrazide	0.33	0.5	4	53	43
11.7	Formamide	4.7	2	91	5	4

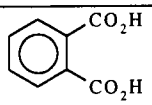
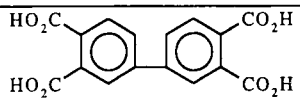
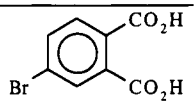
A mixture of hydrazine and formate gave acceptable coupling kinetics but inferior selectivity; indeed their combined effect was only marginally better than that achieved by using formate on its own (see Table 3). As expected hydrazine by itself promoted mostly reduction. The importance of the formyl hydrogen in this chemistry is suggested by the result obtained with oxalyl dihydrazide as reducing agent; this compound can be envisaged as "siamese twin" analogue of **4** bearing no formyl hydrogens. This reagent delivers in theory a double portion of the hydrazine

end of **4**. Our results show that the necessary structural requirements are not met once no formyl hydrogen is present. Not surprisingly, similar results were obtained with acetyl hydrazine. No less rigorous structural demands affect the hydrazide function. Formamide, conceivably a truncated analogue of **4**, promoted mostly reduction. Conversely, N,N'-diformyl hydrazine, albeit providing twice the amount of formyl hydrogens, was a very sluggish coupling promoter. If left a sizable amount of unreacted substrate even after several hours.

The above data show that structural and functional factors find a suitable balance in **4**, making it uniquely effective as a dimerization promoter.

The minimal amount of **4** that allows efficient coupling with **5** as substrate was determined (Table 5). This amount, a little over 0.25 molar equivalents relative to the substrate, implies that all four protons of **4** participate in the catalyst reduction process.

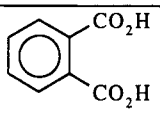
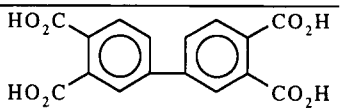
Table 5. Influence of reducing agent to substrate ratio
Conditions : Pd/C 5 %, **4**, 85°C, aq. NaOH

4 to substrate mole ratio	Time (h)	 **6** (a)	 **3** (a)	 **5** (a)
0.33	0.5	10	90	
0.28	0.5	10	90	
0.25	0.5	9	88	3

a) HPLC area %

Substrate purity may not always be uniform between batches. In some cases, slightly lower grades of starting material caused somewhat longer reaction times. In our work, we chose to operate at a marginally higher **4** concentration, thereby offsetting fluctuations in substrate purity and allowing us to work with standardized procedures. Table 6 shows the effect of decreasing the mount of catalyst in the coupling of **5**, at a given concentration of **4**.

Table 6. Effect of catalyst to substrate ratio
Conditions : Pd/C 5 %, **4**, aq. NaOH, 85°C.

Catalyst ratio to 4-BPA (% w/w)	Reaction time (minutes)	 **6** (a)	 **3** (a)
1	15	10	90
0.4	15	10	90
0.2	30	10	90
0.08	180	12	88
0.04	690	15	85

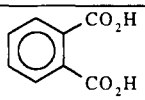
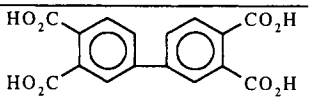
a) HPLC area %

At a certain point (0.08 % w/w catalyst to substrate ratio) there ensued a drop in reaction rate, together with a gradual loss of selectivity. Thus, a treadeoff point was chosen so that a minimal load of catalyst could be used in the process, without an undue sacrifice in rate or selectivity.

A most important issue in the present method was the ability to reuse the catalyst, without losing its activity. This proved to be one of the most salient advantages offered by **4**. Catalyst recovery was straightforward, since it involved a simple filtration step. In our hands, it was possible to perform several cycles of catalyst reuse by simple filtration and washing steps (see Table 7).

Similar experiments using different reducing agents (those appearing in Table 3 and others) resulted in a progressive drop in kinetics from one cycle to the next; this was normally accompanied by a loss in selectivity.

Table 7. Effect of 4 on catalyst recycle
Conditions : Pd/C 5 %, 4, aq. NaOH, 85°C

Catalyst to substrate ratio (% w/w)	Catalyst recycle	Time (h)	 6 (a)	 3 (a)
0.2	0	0.5	10	90
0.2	1	0.5	11	89
0.2	2	0.5	12	88
0.2	3	0.5	10	90
0.2	4	0.5	12	88
0.2	5	0.5	11	89

a) HPLC area %

CONCLUSION

The present work shows that the particular structural properties of formyl hydrazine confer upon it significant advantages over existing reducing agents by : i) inducing high selectivity towards coupling, ii) mediating reactions under mild conditions yet without compromising reaction rates and iii) allowing catalyst recycle. Thus, high yield biaryl coupling of halogenated aromatic compounds can be accomplished by Pd catalyzed dimerization with formyl hydrazine as reducing agent. Due to the cleanness and mildness of the reaction conditions, products of very high purity can be obtained. Since the reactions are carried out in water, processes based on this methodology are economically attractive and product isolation is normally uncomplicated.

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KINETICS AND MECHANISM OF DECOMPOSITION OF N-Br-AMINO ACIDS IN ALKALINE MEDIUM

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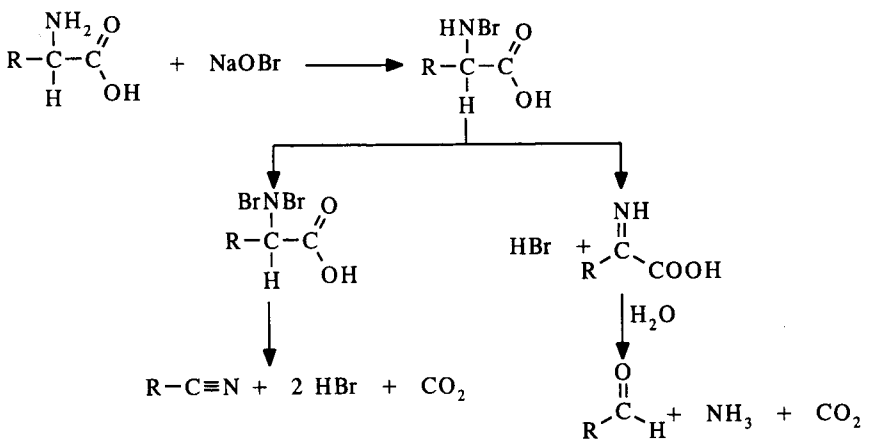
INTRODUCTION

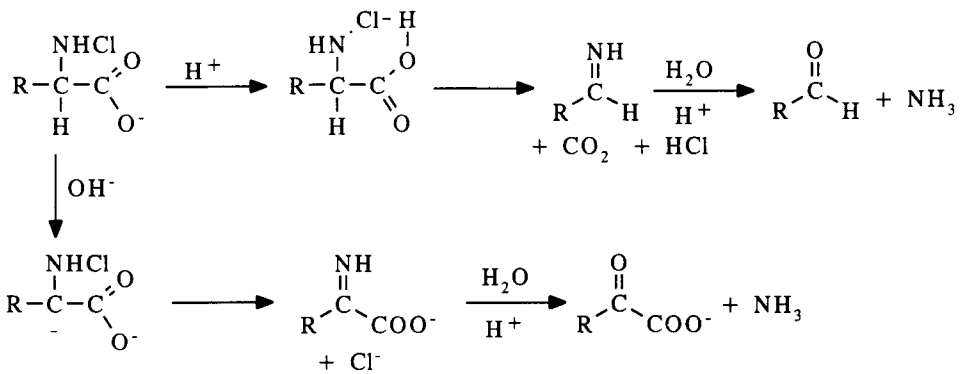
The reaction of aqueous solutions of bromine with amino acids plays an important role in water quality control processes (refs. 1,2) and in the defense of the organisms against infection (refs. 3-5).

N-Bromoamino acids form within seconds after mixing aqueous bromine and the amino acid in dilute aqueous solution (ref. 6), but are not stable end products of the reaction. Thus, Friedman and Morgulis (ref. 7) found that the oxidation of amino acids by hypobromite gives aldehydes and nitriles with one carbon atom less than the original amino acid, ammonia and CO_2 (Scheme 1). The proportions of aldehyde and nitrile depend on the basicity of the medium, aldehyde formation being favoured by more basic conditions.



Scheme 1. Oxidation of amino acids by hypobromite

This mechanism is similar to that proposed by Fox and Bullock (ref. 8) for N-chloroamino acids decomposition in their study of the synthesis of indoleacetic acid by glutamic acid conversion (Scheme 2). They have suggested a path for aldehyde formation consisting of an acid-assisted decarboxylation, yielding an imine that under the conditions of the reaction hydrolyzes to form the corresponding aldehyde. For alkaline media they proposed a mechanism where the α proton is removed from the initial N-chloroamino acid to form a carbanion that immediately stabilizes itself by losing the chloride ion to form the imine intermediate. The final product in this case is an α-ketoacid, and the amount of α-ketoacid formed is related to the basicity of the reaction mixture.



Scheme 2. Decomposition of N-chloroamino acids

More recently Hand et al. (ref. 9) have studied the decomposition reaction of N-chloro-α-amino acid anions in neutral aqueous solution, where the main reaction products are carbon dioxide, chloride ion and imines (which hydrolyze rapidly to amine and carbonyl products). They found that the reaction rate constant of decarboxylation was independent of pH, so they ruled out a proton assisted decarboxylation mechanism, and the one proposed consists of a concerted decarboxylation. For N-bromoamino acids decomposition in the pH interval 9-11 a similar concerted mechanism was proposed by Antelo et al. (ref. 10), where the formation of a nitrenium ion (ref. 11) can be ruled out because it is not consistent with the experimental results. Antelo et al. have also established that when the decomposition reaction takes place at pH < 9, the disproportionation reaction of the N-Br-amino acid becomes important, and the decomposition goes through the N,N-dibromoamino acid. This reaction is also important for N-chloroamino compounds but at more acidic pH values, because the disproportionation reaction

takes place between the protonated and the unprotonated N-chloroamino compound (refs. 12 - 15). In general, the N,N-dihaloamino compounds are the main species when the ratio $[R\text{-}NH_2]/[X_2]$ is lower than 1 or at acidic pH values (refs. 16, 17).

We present here a kinetic study of the decomposition of the N-bromo derivatives of alanine, aminoisobutyric acid and proline in alkaline medium, where the mechanism of decomposition is not fully understood. A discussion of the different microscopic mechanisms that can be proposed is done in the light of the obtained experimental results.

EXPERIMENTAL

Reagents. N-Bromoamino acid solutions were prepared in the spectrophotometer cell by mixing a solution of hypobromite with the corresponding amino acid. Hypobromite solution was prepared by mixing a pH 12 solution of sodium hypochlorite, prepared by bubbling chlorine through NaOH solution, with a solution of potassium bromide (refs. 18, 19). Hypobromite concentration was determined spectrophotometrically (ε_{330} = 324 $M^{-1}cm^{-1}$ (ref. 20)) before use. Proline was supplied by Sigma, and all other reagents were Merck products of the maximum comercially available purity, and were used without further purification.

Kinetic measurements. When the hypobromite solution was mixed with amino acid (in 10-fold excess to avoid formation of N,N-dibromoamino acid) the N-bromoamino acid rapidly formed in accordance with the equation :

$$RCH(NH_2)COOH + HOBr \rightleftharpoons RCH(NHBr)COOH + H_2O \qquad (1)$$

In the spectra of the reaction mixture, the hypobromite absorption band at 330 nm disappeared before the first minute of reaction had elapsed and there appeared an intense band near 290 nm which decreased with time (Fig. 1). On the basis of published information for other N-bromo compounds, this absorption band is attributed to the N-bromoamino acid formed (refs. 6, 21).

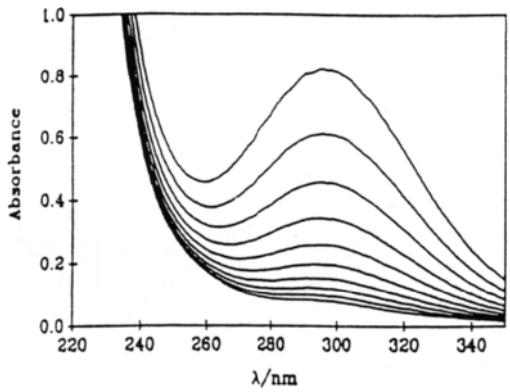


Fig. 1. Spectra of the reaction mixture recorded at various times after mixing of the reagents. [Proline] = 0.02 M, [BrO^-] = 2.0 x 10^{-3} M, [NaOH] = 0.25 M, T = 298 K, t_i = 1.5 s, Δt = 6 s.

The decomposition kinetics of the N-Br-amino acids was studied spectrophotometrically by following the fall in absorbance at the wavelength of the absorbance maximum of the N-bromoamino acid, in a Milton Roy Spectronic 3000 Array or a Beckman DU65 single-beam spectrophotometer, both equipped with a cell carrier thermostated to within ± 0.1 °C by water flow. Kinetic experiments were initiated using a hand-driven HI-TECH SFA-12 Rapid Kinetics Accessory with a 1.00 cm flow cell.

In the case of the decomposition reaction of N-Br-aminoisobutyric acid and N-Br-proline, the absorbance-time data obtained at 289 nm and 293 nm respectively, were well fitted to first order integrated equations :

$$\ln (A - A_\infty) = \ln (A_0 - A_\infty) - kt$$

with correlation coefficients better than 0.9990, following the reaction until at least 80 % complete (Fig. 2). In the case of the decomposition of N-Br-alanine the study of the reaction was done using the initial rate method, because the absorbance-time data obtained at 287 nm were not well fitted to the integrated first order equation. The initial rates used in establishing the kinetic order of this reaction were calculated by fitting straight lines through the first 4-5 % of absorbance-time data by linear regression.

The values reported for the observed reaction rate constants are an average value of those obtained for five experiments, and the data were reproducible within 5 %.

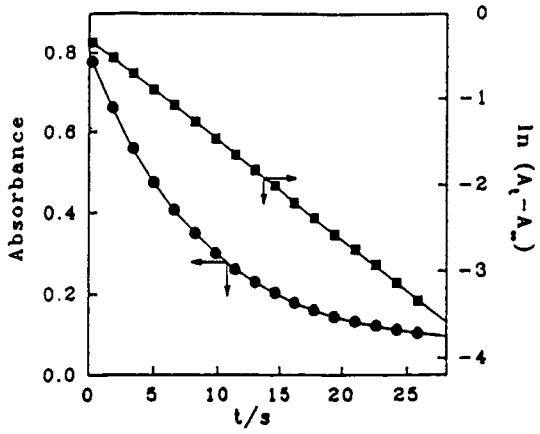


Fig. 2. Absorbance-time graph showing first order compliance for the decomposition reaction of N-Br-aminoisobutyric acid. [BrO^-] = 2.0 x 10^{-3} M, [Aib] = 0.02 M, [NaOH] = 0.25 M, T = 298 K.

KINETIC RESULTS

Order respect to N-Br-amino acid concentration. With the aim of establishing the reaction order with respect to the N-bromoalanine concentration, we have obtained the values of the initial rates for different N-bromoamino acid concentrations with a fixed OH^- concentration of 0.23M. The logarithmic plot shows to be a straight line (Fig. 3) with a slope of 1.07 ± 0.03. This means that the decomposition reaction of N-Br-alanine is first order with respect to the N-bromoalanine concentration. From the plot of initial rate against initial N-bromoalanine concentration (Table 1) we can obtain for the pseudofirst order rate constant for N-bromoalanine decomposition a value of 0.0160 ± 0.0004 s^{-1}.

With a fixed amino acid concentration of 0.02 M, the rate constant proved independent of the concentration of BrO^- over the range (0.38-3.09) x 10^{-3}M for N-Br-aminoisobutyric acid and N-Br-Proline. The plot of the obtained initial absorbance values against the initial N-Br-amino acid conc tration shows that Beer's law is obeyed, and the values for the molar absorptivity of the studied N-bromoamino acids are listed in Table 2.

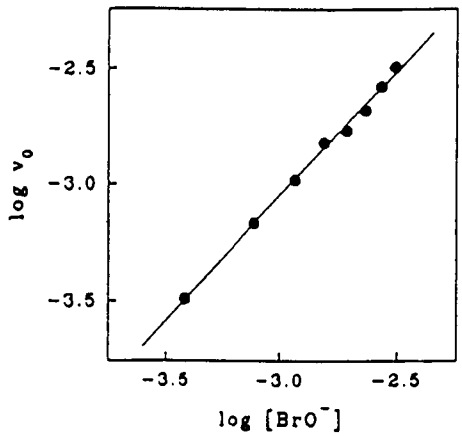


Fig. 3. Logarithmic plot showing compliance with first order rate law respect to N-Br-alanine concentration for the N-Br-alanine decomposition reaction. [Ala] = 0.02 M, [NaOH] = 0.23M, T = 298 K.

Table 1. Initial rate values for N-Br alanine decomposition at different N-Br-alanine concentrations. [Ala] = 0.02M, [NaOH] = 0.23M, T = 298 K.

$[BrO^-]/10^{-3}M$	A_0	$V_0/10^{-6}Ms^{-1}$
0.38	0.163±0.002	5.39 ±0.09
0.77	0.291±0.010	11.3 ±0.6
1.16	0.424±0.017	17 ±1
1.54	0.582±0.009	25.1 ±0.8
1.93	0.702±0.016	28 ±1
2.32	0.838±0.021	35 ±2
2.70	1.008±0.035	44 ±2
3.09	1.174±0.028	53 ±2

Table 2. Molar absorptivities of the studied N-bromoamino acids, $[BrO^-]=(0.38\text{-}3.09)\times10^{-3}$M, [AA]=0.02 M, [NaOH]=0.25 M, T = 298 K

N-Br-Aminoacid	λ_{max}/nm	$\varepsilon/M^{-1}cm^{-1}$
N-Br-Alanine	287	370±7
N-Br-Aminoisobutyric acid	289	400±8
N-Br-Proline	293	406±4

Influence of OH^- concentration on the reaction rate constant. From the dependence of the observed first order rate constant on the sodium hydroxide concentration, shown in Table 3, it can be established that equation (2) holds, where k_0 represents the contribution due to the unimolecular decomposition process and k_{OH} is the contribution due to the base-catalysed process in alkaline medium.

$$\text{rate} = (k_0 + k_{OH}[OH^-])[\text{N-Br-Amino acid}] = k_{obs}[\text{N-Br-Amino acid}] \quad (2)$$

The results obtained for k_0 are, within the experimental error, in accordance with the values obtained in reaction conditions where the main decomposition path is the unimolecular decarboxylation.

It should be noted that the absence of a proton in the α position in the case of N-Br-aminoisobutyric acid makes unoperative its decomposition to form an α-ketoacid, and the slight increase in the observed reaction rate constant upon increasing the NaOH concentration can be attributed to a secondary decomposition process, probably leading to the formation of an hydrazine (refs. 22 - 24).

Table 3. Influence of OH^- concentration on the observed reaction rate constant, [AA]=0.02M, $[BrO^-]=2.06\times10^{-3}$ M, μ=1.0M (KCl), T = 298 K; and results of the linear regression analysis of k_{obs} on [NaOH]

	N-Br-Ala [a]	N-Br-Aib	N-Br-Pro
[NaOH]/M	$k_{obs}/10^{-2}s^{-1}$	k_{obs}/s^{-1}	$k_{obs}/10^{-2}s^{-1}$
0.1	1.18±0.09	0.130±0.001	5.2±0.1
0.2	2.10±0.06	0.131±0.001	6.7±0.1
0.3	2.9±0.1	0.134±0.001	8.2±0.2
0.5	5.3±0.2	0.140±0.001	11.4±0.1
0.7	6.8±0.2	0.148±0.002	14.7±0.2
1.0	10.9±0.3	0.158±0.001	19.7±0.6

N-Br-AMINO ACID	INTERCEPT (k_1/s^{-1})	SLOPE ($k_2/M^{-1}s^{-1}$)
N-Br-Ala	-0.001±0.003	0.106±0.005
N-Br-Aib	0.125±0.001	0.032±0.001
N-Br-Pro	0.035±0.001	0.161±0.001

a) Initial rates

Influence of ionic strength on the reaction rate constant. The influence of the ionic strength on the reaction rate constant was studied using KCl as electrolyte. The results obtained in this study are listed in Table 4, where we can see that the reaction rate constant for N-Br-alanine decomposition undergoes an increment of 40 % upon changing the ionic strength from 0.27M to 1M, while in the case of N-Bromoaminoisobutyric acid the increment of the reaction rate constant is of about 12 %. This is an evidence of a non ionic mechanism in the case of the decomposition of N-Br-aminoisobutyric acid, as it is expected for a concerted decarboxylation mechanism. For the decomposition of N-Br-proline the increase on the reaction rate constant is about 23 % approximately, an intermediate value. This is due to the fact both paths (concerted decarboxylation and elimination) have an important contribution to the total decomposition process.

Table 4 : Dependence of the observed reaction rate constant on the ionic strength (KCl). $[BrO^-]=2.0 \times 10^{-3}$ M, [AA] = 2.0×10^{-2} M, [NaOH] = 0.25M, T = 298 K

	N-Br-Ala a)	N-Br-Aib	N-Br-Pro
μ/M	$k_2/10^{-2}M^{-1}s^{-1}$	$k_{obs}/10^{-1}s^{-1}$	$k_{obs}/10^{-2}s^{-1}$
0.27	7.3±0.3	1.17±0.01	5.34±0.06
0.47	8.9±0.5	1.23±0.01	5.96±0.05
0.67	10.1±0.4	1.26±0.01	6.33±0.05
0.87	10.9±0.2	1.31±0.01	6.81±0.08
1.02	12.2±0.6	1.33±0.01	6.98±0.05

a) Initial rates

Dependence of the reaction rate constant on the temperature. Activation parameters. As we saw in the study of the influence of OH^- concentration on the reaction rate constant, the main path for the decomposition reaction of N-

bromoaminoisobutyric acid is the concerted decarboxylation and for N-bromoalanine the main path of decomposition is the elimination reaction, while for N-Br-proline both paths are important, being the elimination reaction favoured at more basic pH values. Thus, in order to obtain the activation parameters for these two processes we have studied the temperature influence on the reaction rate constant for different NaOH concentrations for the decomposition of N-Br-proline (Fig. 4); and a fixed NaOH concentration of 0.25M for the decomposition of N-Br-alanine and N-Br-aminoisobutyric acid. The pairs of values temperature-rate constant obtained in this study are listed in Table 5 together with the activation parameters.

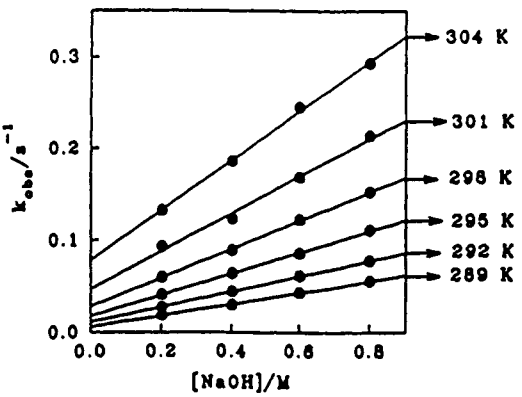


Fig. 4. Influence of NaOH concentration on the reaction rate constant of N-Br-Pro decomposition at different temperatures.
$[BrO^-]$ = 2.0 x 10^{-3} M, [Pro] = 0.02M, μ = 1M (KCl)

Table 5. Influence of temperature on the rate constant. Activation parameters.
- N-Br-Ala, $[BrO^-]=2.0\times10^{-3}$M, [Ala]=0.02M, [NaOH]=0.25M
- N-Br-Aib, $[BrO^-]=2.0\times10^{-3}$M, [Aib]=0.02M, [NaOH]=0.25M
- N-Br-Pro, $[BrO^-]=2.0\times10^{-3}$M, [Pro]=0.02M, [NaOH]=0.25-0.8M, μ=1M(KCl)

	N-Br-Ala	N-Br-Aib	N-Br-Pro	
T/K	$k_2/10^{-2}M^{-1}s^{-1}$	$k_1/10^{-2}s^{-1}$	$k_1/10^{-2}s^{-1}$	$k_2/10^{-2}M^{-1}s^{-1}$
289	3.6±0.2	2.82±0.03	0.61±0.05	6.2±0.1
292	4.5±0.2	4.89±0.03	1.15±0.02	8.3±0.1
295	6.2±0.1	7.51±0.04	1.8±0.1	11.5±0.2
298	7.9±0.3	11.64±0.07	2.9±0.1	15.3±0.2
301	10.4±0.4	17.5±0.2	4.8±0.6	20.4±0.8
304	13.2±0.4	26.7±0.1	7.9±0.3	27.1±0.7

N-Br-AA	React.	E_a/kJ mol^{-1}	$\Delta H^{\neq}$/kJ mol^{-1}	$\Delta S^{\neq}$/kJ mol^{-1}K^{-1}	$\Delta G^{\neq}$/kJ mol^{-1}
N-Br-Ala	(ii)	64 ±1	62 ±1	-59 ±4	79.6
N-Br-Aib	(i)	108 ±2	106 ±2	92 ±6	78.6
N-Br-Pro	(i)	122 ±2	119 ±2	127 ±8	81.2
N-Br-Pro	(ii)	72.0 ±0.5	69.5 ±0.5	-27 ±2	77.5

DISCUSSION

Upon mixing the amino acid and hypobromite solutions, the corresponding N-Br-amino acid is formed very rapidly. The following acid-base equilibria are established in the reaction medium :

$$\underset{\mathbf{1}}{BrH_2N^+CH(R)COOH} \overset{K_3}{\rightleftharpoons} \underset{\mathbf{2}}{BrHNCH(R)COOH} + H^+ \quad (3)$$

$$BrHNCH(R)COOH \overset{K_4}{\rightleftharpoons} \underset{\mathbf{3}}{BrHNCH(R)COO^-} + H^+ \quad (4)$$

for N-Br-alanine and N-Br-proline an additional equilibrium process must be considered :

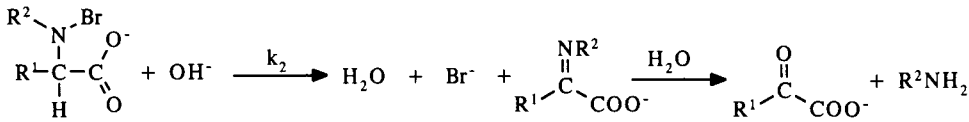
$$BrHNCH(R)COO^- + OH^- \overset{K_5}{\rightleftharpoons} \underset{\mathbf{4}}{BrHNC^-(R)COO^-} + H_2O \quad (5)$$

Though no values have been published for K_3, K_4 and K_5, available information for analogous compounds suggests (a) that the N-Br bond ought not to have much effect on the pK_a of the carboxyl group, i.e., pK_4 should be about the same as the pK_a of the carboxyl group of the corresponding amino acid (2.35, 1.95, 2.36 for alanine, proline and aminoisobutyric acid respectively (ref. 25)), (b) that the amino group ought to become much more acid than in the unbrominated amino acid, with the data for secondary N-Br-amines (ref. 26) suggesting that $pK_3 < 3$, and (c) that the bromine atom bonded to nitrogen ought to have little effect on the pK_a of the α-methine hydrogen, i.e., $pK_a \sim 16$ (ref. 27). The predominant species in alkaline media should therefore be **3**. In accordance with the experimental results, two reaction mechanisms are suggested as acting under these conditions, a

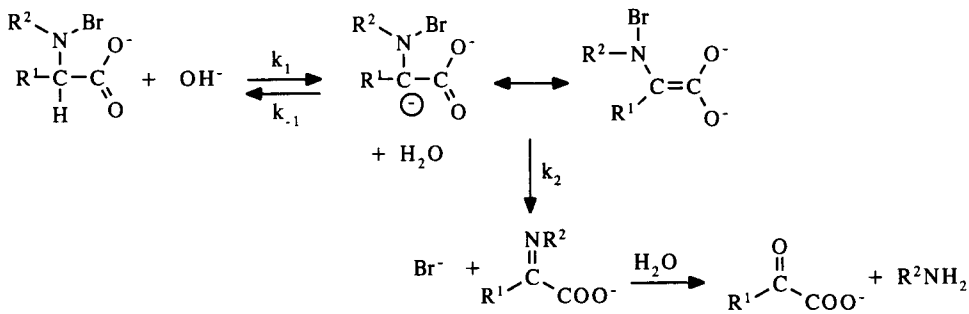
concerted decarboxylation and a base catalyzed elimination; being the former the main decomposition path for N-Br-aminoisobutyric acid and the latter the main decomposition path for N-Br-alanine. In the case of N-Br-proline both paths are competitive, being the elimination reaction favoured at more basic conditions.

The mechanistic possibilities for the imine formation by a base-promoted 1,2-elimination reaction are shown in Scheme 3.

Concerted mechanism



Stepwise mechanism



Scheme 3. Mechanistic possibilities for the imine formation

Considering the stepwise mechanism, different possibilities arise depending on the relative values for the rate constants k_1, k_{-1} and k_2. The application of the steady state condition to the carbanion yields equation (6) for the rate constant of the basic catalysis process.

$$k_{OH} = \frac{k_1 k_2}{k_{-1} + k_2} \qquad (6)$$

As $k_2 << k_{-1}$, this leads to

$$k_{OH} = \frac{k_2 k_1}{k_{-1}} = K_1 k_2 \qquad (7)$$

which means that the reaction involves a rapid preequilibrium step followed by a slow unimolecular elimination from the carbanion. This mechanism, termed reversible E1cB, is characterized by the absence of isotope effect. For a similar elimination reaction leading to the formation of imines from N-halobenzylalkylamines, Cho et al. (ref. 28) have found the existence of an isotope effect of 6, similar to that found by Armesto et al. for the decomposition of N-Cl-glycine (ref. 29), which let us rule out this mechanistic possibility.

If $k_2 >> k_{-1}$, then $k_{-1} + k_2 = k_2$, and $k_{OH} = k_1$. In this case there are two alternative possibilities : (a) The formation of a stable carbanion in the rate limiting step, being the elimination of the leaving group the fast step (irreversible E1cB mechanism), and (b) the concerted E2 elimination mechanism, where the elimination of the leaving group and the proton abstraction are concerted, but not necessarily synchronized (concerted mechanism in Scheme 3). In the case (a) the presence of electron-withdrawing groups in the molecule will enhance the rate, and as the chlorine atom is more electronegative than the bromine, the decomposition of the N-chloro derivative is expected to be faster than the decomposition of the corresponding N-bromo derivative. The values of k_{OH} for the decomposition of N-chloroproline and N-bromoproline are 0.0321 $M^{-1}s^{-1}$ and 0.161 $M^{-1}s^{-1}$ respectively, showing an opposite behaviour to what it was expected, so this mechanism can be ruled out. A very effective method for visualizing all these mechanistic possibilities is to use a More O'Ferrall diagram (refs. 30, 31). For these reaction-coordinate diagrams, elimination reactions have proton removal as the abscisa, leaving group loss as the ordinate, and free energy as the third coordinate (Figure 5). A diagonal connection between the reactants and products represents a synchronous E2 process, and the opposite corners represent the E1 and E1cB mechanistic extremes.

The effect of the leaving group (k_{Br}/k_{Cl}) can be a useful tool to obtain information about the relative extent of N-X bond cleavage in the transition state. Thus, if the route from the N-haloaminoacid (bottom left) to the imine (top right) involves first the breaking of the C-H bond and then the loss of the halide ion by the resulting carbanion (bottom right), k_{Br}/k_{Cl} ought to be close to unity, since the identity of the halogen only influences the process at a late stage, during the breaking of the N-X bond. If, on the other hand, it is the N-X bond that is broken first, to give a nitrenium ion (top left) which then loses the α proton to yield the imine, the stability of the N-X bond should have a greater effect on the reaction rate, and the value of k_{Br}/k_{Cl} should be much greater than unity.

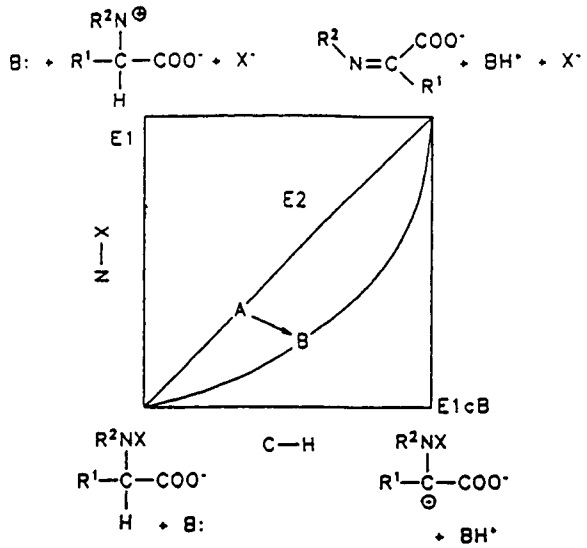


Fig. 5. More O'Ferrall diagram for base-promoted, imine forming 1,2-elimination reactions.

For elimination from $ArCH(R)N(X)CH_3$ promoted by MeONa-MeOH Hoffman et al. (ref. 32) have found a leaving group effect ranging from 28.8 for R = Me to 11.1 for R = Ph; being attributed this variation to the decrease in the extension of the leaving-group loss in the transition state. In a qualitative way they have located the transition states of these three derivatives in a More O'Ferrall-Jencks diagram, being assigned the more central transition state (point A in Fig. 5) to R = H, for which k_{Br}/k_{Cl} = 11.8. In the case of the N-bromoproline decomposition reaction the value of k_{Br}/k_{Cl} is 5.0, which means that the reaction goes through a transition state with a higher carbanionic character (point B in Fig. 5). This carbanionic character of the transition state can be rationalized in terms of an important contribution of the carbanionic intermediate, stabilized by resonance (Scheme 3).

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ARYLATION OF HARD HETEROATOMIC NUCLEOPHILES USING BROMOARENES SUBSTRATES AND Cu, Ni, Pd-CATALYSTS

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SUMMARY

The arylation of different hard heteroatomic nucleophiles with arylbromides has been investigated using Pd, Ni or Cu-catalysts.

The reaction of arylbromides with amines affords mostly the corresponding aromatic hydrocarbon by using palladium catalysts, but the expected substituted anilines are formed in good yields by using a nickel (II) catalyst.

The reaction of alcohols with arylbromides and nickel or copper catalysts, in presence of base, has been investigated comparatively in regard to the influence of the metals, of the ligands, of the base, of the primary or secondary alcohols and of the substituents on the arylbromide. The best conditions, with bipy$NiBr_2$ in presence of $KHCO_3$ at 125°C, afford quantitative yields in the phenylalkyl ethers from the primary alcohols.

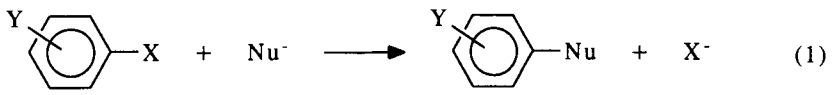
The hydrolysis of arylhalides into phenolate, actually the arylation of hydroxide anion, has also been investigated by using copper catalysts. As for the arylation of alcohols, the bromobenzene is much more reactive than the chlorobenzene. The reaction needs an induction period which depends strongly on the temperature and less significantly on the copper catalyst. From the results obtained in presence of different radical scavengers or reductors, a new mechanism has been proposed for the hydrolysis of the arylhalides, including a preliminary redox process leading to a copper (I) species and then a radical free catalytic cycle, corresponding to oxidative addition and reductive elimination processes.

Last, the nickel catalyzed halogen exchange for haloarenes, actually the arylation of halide anions, has been investigated. The equilibrated exchange between the phenyl bromide (60 %) and the phenyliodide (40 %) allows with some

nucleophiles a co-catalysis system in which the bromobenzene is used as arylating agent in presence of 0.1 equivalent of sodium iodide.

All these transformations show that the arylbromides can exhibit a diversified reactivity as arylating agents by using metallic catalysts.

The fundamental and pratical importance of arylation, particularly the arylation of heteroatomic nucleophiles, was several times emphasized in the last few years (refs. 1, 2) (eqn. 1).



(1)

X = I, Br, Cl, (F)

In such arylations, the entering nucleophile can have different nature, but very often the leaving group X represents an halogen.

The principal mechanisms for the nucleophilic arylation by aromatic halides are :

- first, the classical nucleophilic aromatic substitution (S_NAr), which is the result of an initial addition of the nucleophile on the ipso carbon leading to the anionic Meisenheimer adduct as intermediate;
- the second mechanism which can be encountered is the benzyne mechanism, needing generally a strong basic nucleophile in order to attack an hydrogen on the ortho position and to eliminate the leaving group;
- further, the $S_{RN}1$ mechanism proceeds through a radical anion formed by a monoelectronic transfer from the nucleophile to the conjugated aromatic system;
- the last mechanism (Fig. 1) involves a transition metal M, such as nickel, copper or palladium as catalyst, which is inserted by an oxidative addition into the carbon-halogen bond.

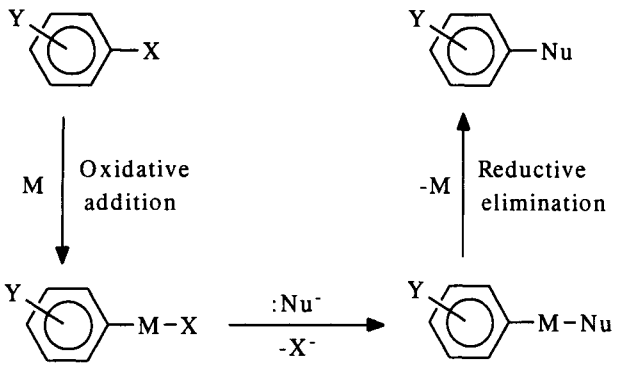
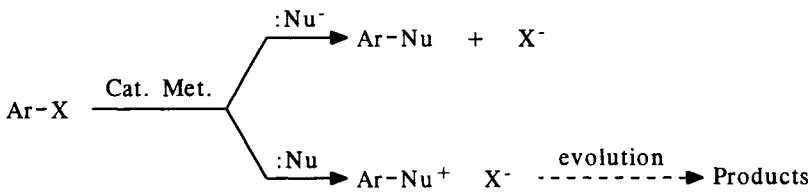


Fig. 1. Arylation of nucleophiles catalyzed by metallic complexes M

This last arylation mechanisms is specially interesting because :
- first, it does not need any particular activating Y substituent on the aromatic ring;
- further, the substitution proceeds with full regio-selectivity on the ipso carbon.

The results presented in this review concern this metal-catalyzed mechanism.

Depending on the nature, anionic or neutral, of the different nucleophiles, the result of the arylation can be a neutral substitution product or a cationic one, which most often, in the last case, undergoes an evolution, for example (starting form a phosphite) to a phosphonate or, after deprotonation, to an arylamine or to an arylether (Fig. 2).



(ArI > ArBr > ArCl >> ArF)

:Nu⁻ or :Nu		Soft								Hard			
		Cl^- BR^- I^-	CN^-	$^-C{\equiv}CR$	$^-CH_2COR$	^-SR	^-SeR	R_3P	$(RO)_3P$	HNR_2	^-OR	^-OH	^-OPh
Met.	Co	(3) *						(9)		(3)			
	Ni	(3),(4)	(5)	(2)	(2)	(2)	(2)	(4),(9)	(11)	(3),(7)			(3)
	Pd	(4)	(6)	(2)	(8)	(2)		(4),(10)	(12)				
	Cu	(13)	(13)	(13)	(13)	(13)		(13)	(13)	(13)	(13)	(13)	(13)

* Literature reference

Fig. 2. Arylations of nucleophiles described in the literature

Such arylations are characterized by a general order of leaving group ability in which the bromine is better than chlorine and much more than fluorine. Therefore, such catalytic reactions seem to be well adapted for a synthetic use of aryl bromides.

As shown in this table, the metal catalysts used in the literature are mostly complexes of Ni or Cu and less often Co or Pd. For soft nucleophiles, on the left of the table, the efficiency of the nickel catalysts was already reported[2]. Here, are presented the investigations concerning the arylation of hard nucleophiles such as amines, alcohols or hydroxide anion, using Ni, Pd and Cu catalysts.

Arylation of amines or alcohols catalyzed with copper are well documented (Fig. 3).

$$ArX + HNR_2 \xrightarrow{[Cat.Cu]} ArNR_2 + HX$$

R = H, Alk, Ar, COR' (GOLDERG), SO_2R

$$ArX + MOR \xrightarrow{[Cat.Cu]} ArOR + MX$$

R = H, Alk, Ar (ULLMANN)

$$Nu^- + CuY \xrightarrow[\text{irreversible}]{\text{fast}} CuNu + Y^-$$

$$CuNu + ArX \xrightarrow{\text{slow}} ArNu + CuX$$

Fig. 3. Arylation of amines or alcohols catalyzed by copper

With ammonia (refs. 14 - 25), alkyl (refs. 26 - 28) or arylamines (refs. 29 - 44) as well with amides (refs. 37,45-49) (the Goldberg reaction (ref. 50)) the reaction affords substituted anilines.

With alcohols or more often with alcoholates (refs. 51 - 56) or phenolates (refs. 57 - 64) the arylethers are formed. Typically, one of the Ullmann reactions is corresponding to the diarylethers synthesis.

The hydrolysis reaction with sodium or potassium hydroxide affords the corresponding phenols (refs. 65 - 68).

For such reactions, the formation in the first step of a Cu(I) Nu species is generally accepted. But, for the arylation step four different mechanisms have been proposed (ref. 69) :

- a free radical mechanism
- a concerted four center mechanism
- an organocuprate π-complex
- and, an oxidative-addition / reductive elimination mechanism.

This last one is now generally well accepted for the nickel catalysis.

The mechanism of the nickel (0) catalyzed arylation of nucleophiles corresponds to this catalytic cycle according mostly to the results of Kochi (ref. 70) (Fig. 4).

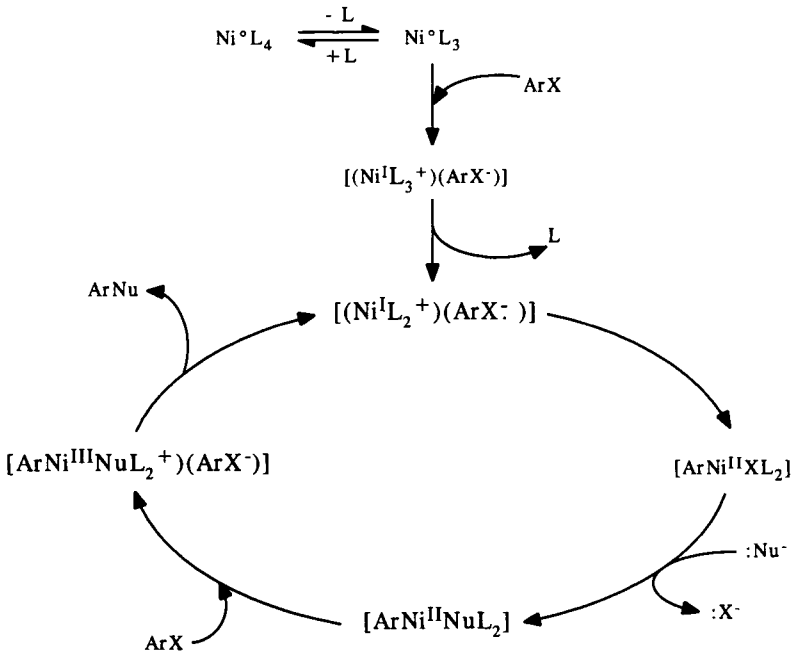


Fig. 4. Mechanism of the arylation catalyzed by the nickel (0) complexes

This cycle involves, first, a monoelectronic transfer from the nickel (0) complex to the aryl halide affording a Ni(I) complex and then an oxidative addition affording a 16 electron-nickel (II) which undergoes a nucleophilic substitution of : Nu^-, then a monoelectronic transfer occurs once again with a second aryl halide, and, last, a reductive elimination of the arylated nucleophile regenerates the active Ni(I) species.

We have investigated the arylation of different primary or secondary amines with different aryl chlorides or bromides in heterogeneous or homogeneous catalysis conditions using palladium(0) or palladium(II) derivatives (Fig. 5).

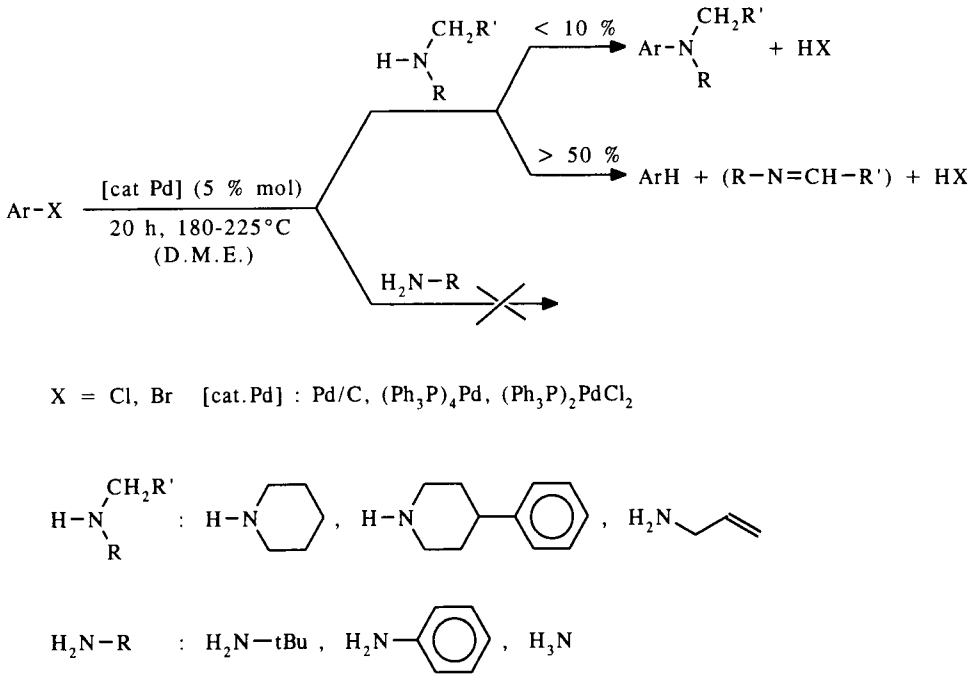


Fig. 5. Arylation of amines catalyzed by Palladium complexes

For the amines without hydrogen on the carbon α to the nitrogen, no reaction takes place in spite of the quite high temperatures used. But, with the primary or secondary amines bearing an hydrogen on the carbon α to the nitrogen, the arylation yields are generally very low, lower than 10 % in the corresponding arylamine. On the contrary, the major part of the aryl halide is reduced to the corresponding aromatic hydrocarbon with simultaneous formation of an imine, which undergoes different evolution to typical end-products, depending on the starting amine.

The reduction of aryl halide can be probably explained according to the following catalytic cycle (Fig. 6).

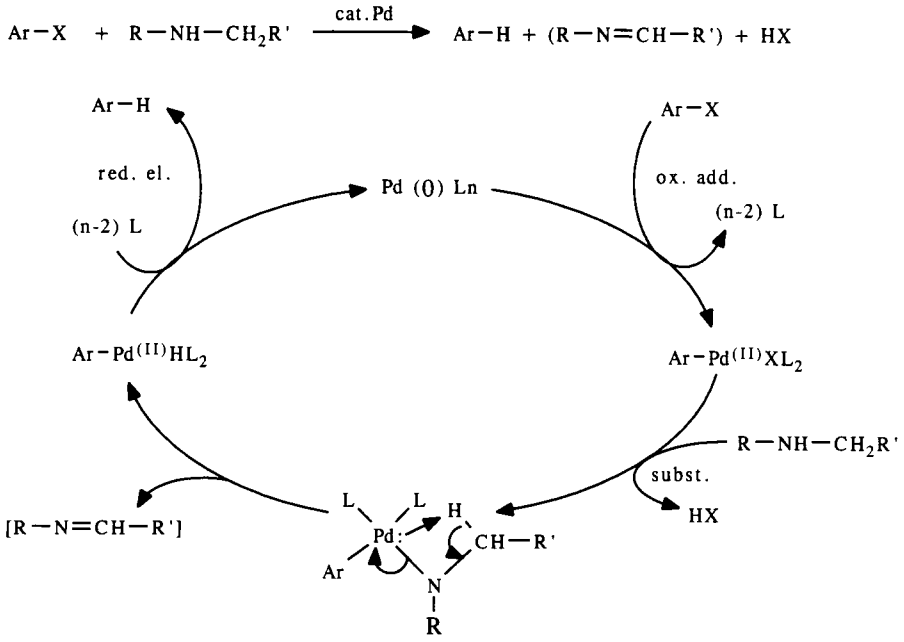
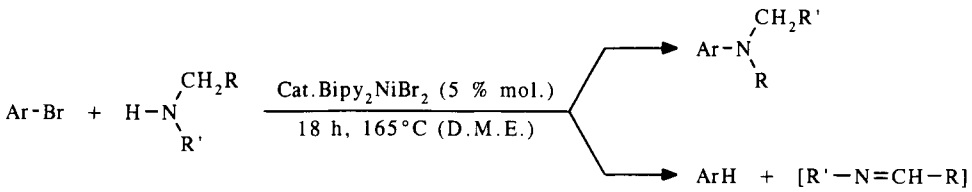


Fig. 6. Attempted mechanism for the reduction of haloarenes

The palladium(0) complex undergoes first an oxydative addition of the aryl halide. Then a substitution reaction of the halide anion by the amine occurs at the metal. The resulting amino-complex would lose the imine with simultaneous formation of an hydropalladium. A reductive elimination from this 18-electrons complex would give the aromatic hydrocarbon and regenerate at the same time the initial catalyst.

If, instead of a palladium catalyst, a nickel catalyst, such as the bipyridylnickel(II) bromide, is used for the arylation of amines (Fig. 7), the reduction of the aryl halide into the corresponding aromatic hydrocarbon is still present for the primary or secondary benzylamines; but, the arylation into substituted anilines is the main reaction even most often the only one, for the other types of amines.

It is very likely that the difference between the nickel and palladium-catalysts corresponds to the reductive character or to the hydrogene affinity, less important for the nickel than for the palladium.



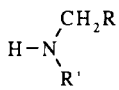
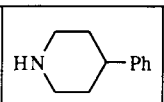
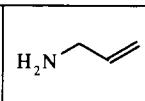
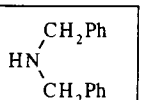
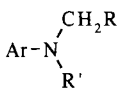
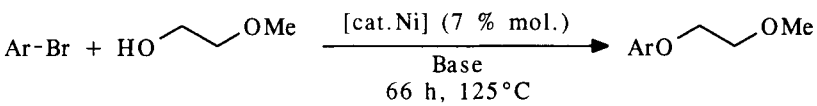
				H_2N-CH_2Ph	
	95 %	77 %	75 %	46 %	/
Ar-H	/	/	/	29 %	36 %

Fig. 7. Arylation of amines catalyzed by nickel catalysts

Therefore, for the arylation of oxygenated nucleophiles, particularly of the alcohols, the investigations were focused on the nickel catalysts (Fig. 8).



Cat.	Base (equiv. mol.)	Yield (%)
/	nPr_3N (4)	/
$bipy_2NiBr_2$	/	/
$bipy_2NiBr_2$	nPr_3N (4)	80

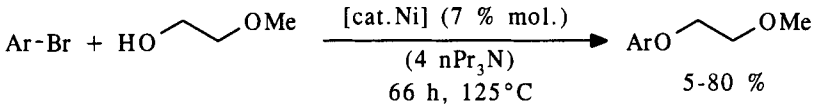
Fig. 8. Arylation of alcohols catalyzed by nickel catalysts

The two first experiments have been performed without a metallic catalyst or without base. In both cases, the arylation reaction does not take place to give the corresponding aromatic ether.

But in the presence simultaneously of a nickel catalyst and of a tertiary amine, the aryl bromide is activated and the bromhydric acid fixed, in such a way to give a very good yield (80 %) in aryl ether in regard to the moderate temperature

conditions (125°C) of the reaction and to the use of an alcohol (not the corresponding alcoholate) as a nucleophile.

The comparison of several nickel catalyst for the arylation of alcohols with arylbromide has been performed, in the same conditions of time, temperature and base, using different oxygen, phosphorus and nitrogen ligands. The yields for each catalyst, shown in the table (Fig. 9) range from 5 to 80 %.



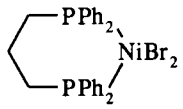
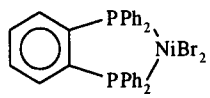
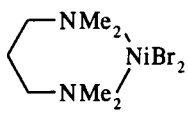
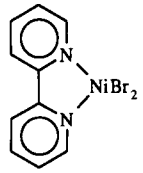
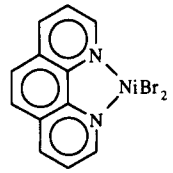
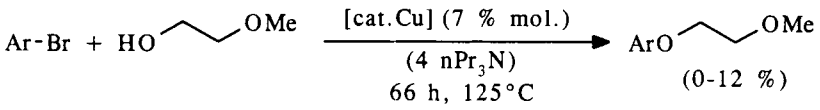
Ligand	Catalyst / Yield (%)		
O	$NiBr_2$	$Ni(acac)_2$	$Ni(OAc)_2$
	37	8	6
P			$Ni(PPh_3)_4$
	21	14	5
N			
	11	80	31

Fig. 9. Influence of the Nickel catalysts on the arylation of alcohols

The bipyridyl ligand, with 80 %, gives the best catalyst, probably because it affords the best balance between the σ-donor and π-acceptor characters which favours respectively the oxidative addition of the aryl bromide and the reductive elimination of the aryl ether at the nickel center.

It is interesting to point out that the same kind of arylation of this methoxyethanol with arylbromide, performed in the same reactions conditions, but now in presence of copper(I) or (II) catalysts with oxygen, phosphorus or nitrogen ligands give very poor yields no higher than 12 % in aryl ether (Fig. 10).



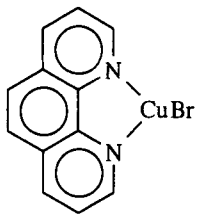
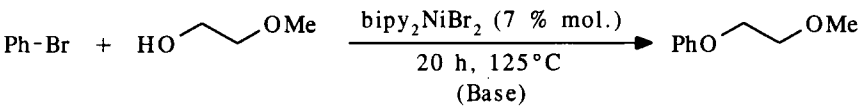
Ligand	Catalyst / Yield (%)			
O	CuBr	$CuBr_2$	$Cu(acac)_2$	$Cu(OAc)_2$
	4	/	6	12
P or N	$CuCl(PPh_3)_3$			
	/		/	

Fig. 10. Influence of the Copper catalysts on the arylation of alcohols

These results point out, for the arylation of alcohols, a better activity of the nickel catalysts in comparison to the copper analogs. That might be probably connected to the harder character of nickel(II) complexes in comparison to the copper analogs.

The arylation of the methoxyethanol with the bromobenzene was investigated changing the nature of the base (Fig. 11), but using the bipyridylnickel catalyst, a shorter time, and keeping the same temperature.

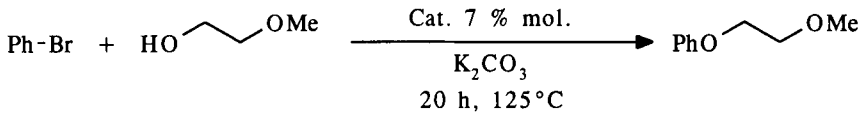
From the different organic and inorganic bases, the monopotassium carbonate appears as the best one, affording a quantitative yield in aryl ether.



Base	nPr_3N	K_2CO_3	$KHCO_3$	KOAc
Yield (%)	23	70	100	10

Fig. 11. Influence of the base on the Nickel catalyzed arylation of alcohols

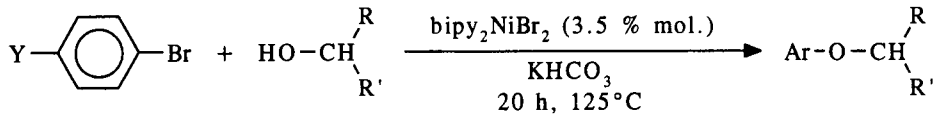
A new comparison of the copper and nickel catalysts (Fig. 12) on the arylation of alcohols, using potassium carbonate as base, shows once again the superiority of the nickel catalyst (70 % against 40 % for the copper catalyst).



Cat.	CuBr	$Bipy_2NiBr_2$
Yield (%)	40	70

Fig. 12. Comparison of the Copper and Nickel catalysis on the arylation of alcohols

Now using the best experimental conditions, it was possible to investigate raughly the scope and limitations of the arylation of alcohols regarding both the substrates : the alcohol on one hand and the arylbromide on the other one (Fig. 13).



Alcohol	R	CH_2OMe	nPr	nPr	nPr	nPr
	R'	H	H	H	H	Me
ArBr	Y	H	H	OMe	OH	H
Yield (%)		100	100	90	0	40 (7d, 125°C)

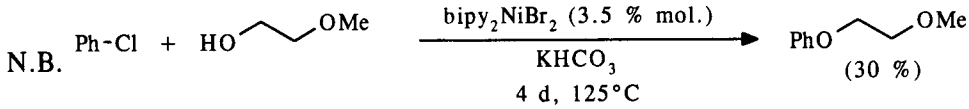


Fig. 13. Influence of the substrates on the arylation of alcohols

The alcohol can be primary or secondary : the arylation with bromobenzene (Y is an hydrogen) affords quantitative yields with the primary alcohols but only 40 %, even after a longer time, with the 2-pentanol as secondary alcohol.

Concerning the arylbromide, the para-substituents Y play an important role : as expected and as shown in the table (Fig. 13) for the arylation of 1-butanol, the electron donating substituent lowers the yield but only to 90 % for the methoxy substituent; on the contrary the hydroxy substituent inhibits fully the arylation owing probably to the much higher electron donating character of this group in the basic conditions used.

It is noteworthy to point out once more the much higher reactivity of the bromobenzene compared to the chlorobenzene : the chlorobenzene affords only 30 % of the phenyl ether after 4 days, whereas the bromobenzene gives already 100 % after only 20 hours.

In connexion with the arylation of hard nucleophiles, it was interesting to reinvestigate the hydrolysis of arylhalides in presence of copper catalysts, which is in fact the arylation of hydroxide anion and represents an important industrial challenge (eqn. 2).

$$Ar\text{-}X + Na^+ OH^- \xrightarrow{[cat.Cu]} Ar\text{-}OH + Na^+ X^- \qquad (2)$$

The results for the hydrolysis of chlorobenzene, o-chlorotoluene and p-chloroanisole in presence of cuprous oxide at different temperatures (Fig. 14) show a good selectivity for the reaction of the chlorobenzene. But, the p-chloroanisole is also transformed by a secondary demethylation reaction into the corresponding p-chlorophenolate.

Nevertheless, the results show that, as expected, the electron-donating substituents disfavour the arylation reaction and the increase of temperature favours the hydrolysis.

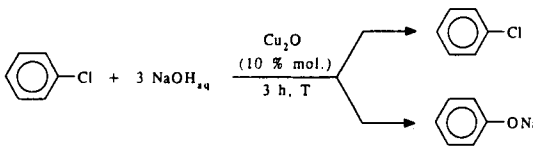
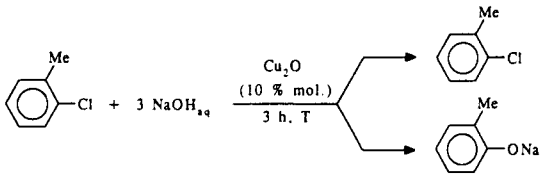
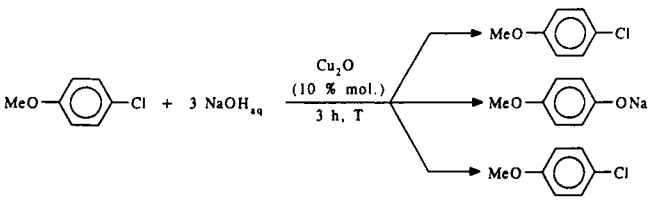
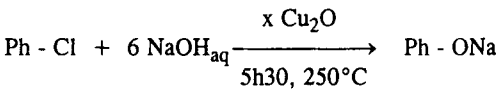
	230°C	250°C
	83.6 9.7	69.5 24.3
	87.5 1.6	66.1 20.8
	63.9 5.5 17.3	40.7 5.8 39.4

Fig. 14. Influence of the temperature and substrates on the hydrolysis of chloroarenes

The influence of the copper catalyst ratio on the hydrolysis of arylhalide has been investigated on the chlorobenzene. The yield of the phenolate formation in these reaction conditions is depending on the initial molar ratio of the cuprous oxide to the starting chlorobenzene (Fig. 15).



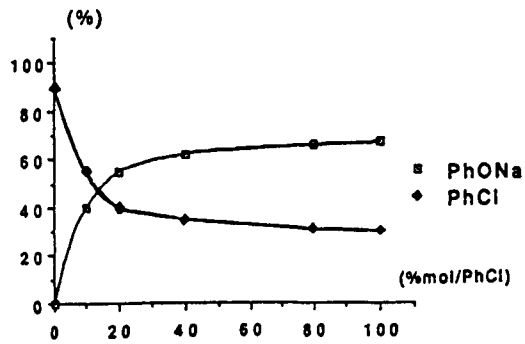


Fig. 15. Influence of the Copper catalyst ratio on the hydrolysis of chlorobenzene

As shown by the curve the transformation yield is almost maximum for a molar ratio of 40 % in cuprous oxide and does not increase significantly for higher quantities of the catalyst. The best operating ratio seems to be between 5 and 10 % moles of cuprous oxide in regard to the chlorobenzene.

By comparison of the hydrolysis rate for the chloro- and bromobenzene catalyzed with cuprous oxide (Fig. 16), it is easy to show that the reactivity of bromobenzene as arylating agent is much higher than the reactivity of chlorobenzene : the yields in phenolate is higher than 90 % after half an hour at 230°C for the bromobenzene whereas the chlorobenzene affords only about 65 % after 15 hours, even at higher temperature (250°C).

$$Ph\text{-}X + 3\,NaOH_{aq} \xrightarrow[t\,(h),\,T°C]{Cu_2O\ (10\ \%\ mol.)} Ph\text{-}ONa + NaX + H_2O$$

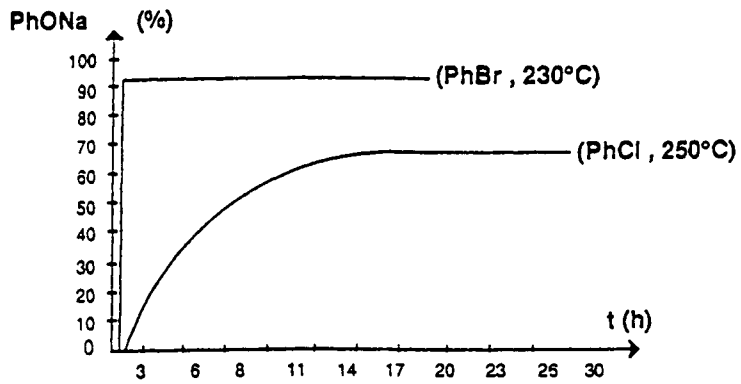
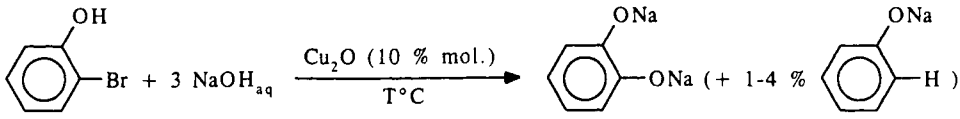


Fig. 16. Comparison of the hydrolysis rate for chloro- and bromobenzene

According to their difference in reactivity both chloro- and bromobenzene are good model-substrates in order to point out more significantly the influence of several reactions factors, depending on the magnitude of this influence.

Last, it must be pointed out in this investigation a characteristic feature : before the reaction starts, the hydrolysis rate needs a short induction period, about 1 hour for the chlorobenzene and 0.5 hour for the bromobenzene.

The investigation on the influence of the temperature on the hydrolysis rate of the ortho-bromophenol into the catecholate shows that the induction time depends strongly on the temperature from about 5 hours at 135°C to 1 hour at 165°C and 1/2 hour at 180°C (Fig. 17).



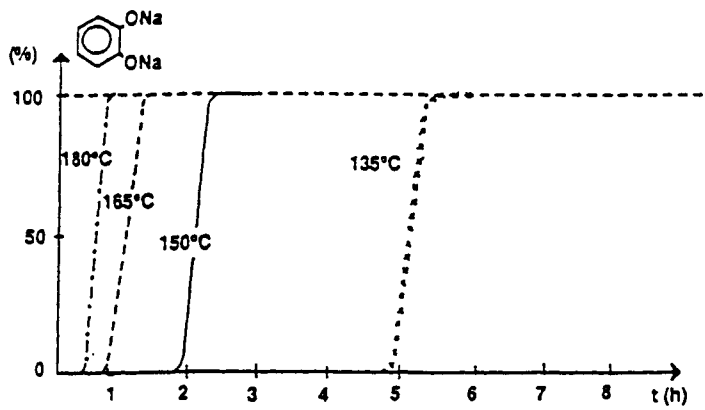


Fig. 17. Influence of the temperature on the hydrolysis rate of the 2-bromophenol

But, after the induction period, the hydrolytic transformation into catecholate is very fast, within 5 to 10 minutes in all the cases.

In the same way, the correlation of the nature of the copper catalyst with the rate of the hydrolysis of bromobenzene exhibits in all cases an induction time of about 1 hour, and a transformation time of 10 to 40 minutes (Fig. 18).

The copper catalysts can be :

- either, metallic copper(0), with or without additionnal sodium bromide;
- or, the copper(I) or copper(II) oxides or bromides.

$$Ph\text{-}Br + 3\,NaOH_{aq} \xrightarrow[230°C]{20\ \%\ mol.\ [Cat.Cu]} PhONa + NaBr + H_2O$$

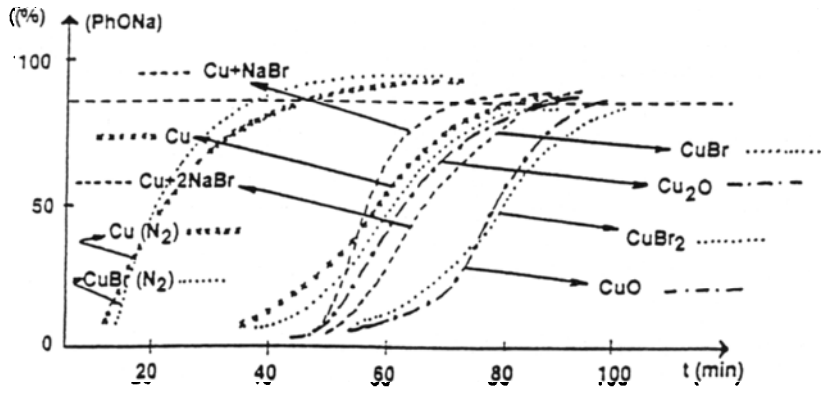
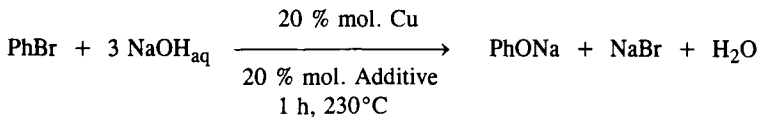


Fig. 18. Influence of the Copper catalyst on the hydrolysis of bromobenzene

It is noteworthy that metallic copper or cuprous bromide used under nitrogen atmosphere shows only a very short induction time. This last result points out the inhibitor role of the oxygen of the air atmosphere and most likely the important role taken either by reduced species or by radical intermediates in the catalytic cycle.

In order to check more exactly these conclusions, various additives were used under normal air atmosphere (Fig. 19).

These additives can have essentially a reductive character such as the Zn powder or a radical trapping character such as p-dinitrobenzene, triphenylphosphine, p-diaminobenzene, di-tertiobutylphenol or both characters in the case of hydroquinone.



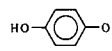
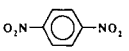
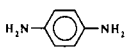
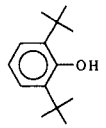
PhBr (%)	85.2	47.4	42.6	17.3	11.9	5.8	5.6
PhOH (%)	7.3	46.3	50.2	66.2	84.7	90.7	91.4
Additive		Zn			Ph_3P		

Fig. 19. Influence of additives on the hydrolysis of bromobenzene

In comparison to the normal reaction without additive which affords a yield of 50.2 % in phenol, the additives on the right part of the table reduce the induction time probably by trapping more or less efficiently the air-oxygen inhibitor.

But, the increasing of the yields, in this case, shows that the catalytic cycle does not involve any radical species which can be trapped. Therefore the hydroquinone inhibition is probably connected with a sensitive redox process in the activation phase.

According to these conclusions, it is possible to propose a catalytic cycle (Fig. 20) involving no radical species, but a copper(I) complex with the classical oxidative addition, nucleophilic substitution and reductive elimination resulting lastly in the arylated nucleophile.

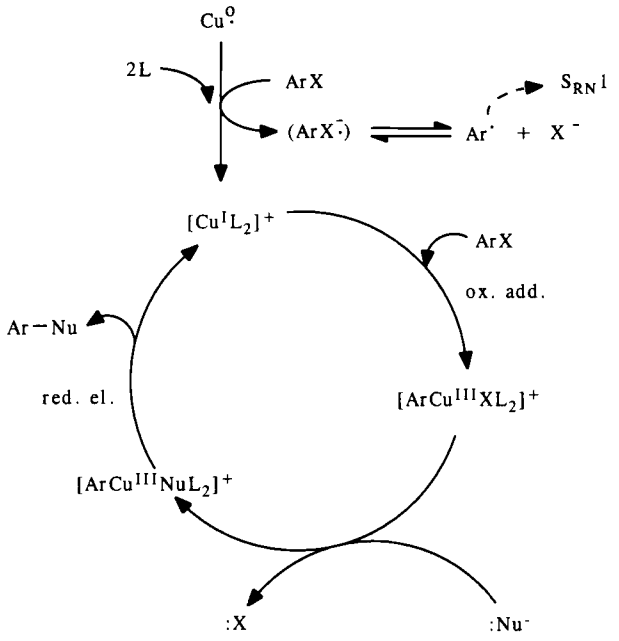


Fig. 20. Attempted mechanism for the arylation catalyzed by the copper complexes

In this case the decisive redox process, which would be specifically inhibited by the hydroquinone, would be the formation of the copper(I) complex corresponding to a monoelectronic transfer from copper(0) to the aryl halide.

Normally, the radical anion could be the starting point for a competitive $S_{RN}1$ process leading also to the same arylated nucleophile but the presence of radical scavengers, such as dinitrobenzene or ditertiobutylphenol would inhibit this secondary way of arylation, increasing the overall yield of arylation.

This mechanistic hypothesis which agrees with the last results obtained by Dominique Nobel (ref. 56) would certainly need much more investigations to be corroborated.

In the last part of this account it is interesting to change to another kind of arylation, which is also important from the preparative point of view.

It is the metal catalyzed halogen exchange for haloarenes, that is to say the arylation of halides anions (chloride, bromide, iodide), acting as nucleophiles (Fig. 21).

$$Ar\text{-}X + Q^+ X'^- \underset{}{\overset{[Cat.]}{\rightleftharpoons}} Ar\text{-}X' + Q^+ X^-$$

(X, X' : Cl, Br, I)

[Cat.] : $NiBr_2$, $bipy_2NiBr_2$, $Ni(PPh_3)_4$, $Ni(cod)_2$
CuX , Cu_2O , CuX_2

$$\underset{(60\ \%)}{Ph\text{-}Br} \overset{[Cat.Ni]}{\underset{200°C}{\rightleftharpoons}} \underset{(40\ \%)}{Ph\text{-}I} \qquad \underset{(95\ \%)}{Ph\text{-}Cl} \overset{[Cat.Ni]}{\underset{200°C}{\rightleftharpoons}} \underset{(5\ \%)}{Ph\text{-}I}$$

Fig. 21. Metal - catalyzed halogen exchange for haloarenes

Some results are already described in the literature with nickel- or copper catalysts (refs. 3,71-78). It was us possible to develop this exchange and to show that it is under thermodynamic control : the equilibrium lies about 60 to 40 % for bromine and iodine, and is much more shifted to the left (95 to 5 %) for chlorine and iodine.

This exchange can in fact be used to change the pratical reactivity of the bromo compounds.

In a co-catalysis system (Fig. 22) the bromobenzene used as arylating substrate is first transformed partly through the reversible halogene exchange with iodide anions into iodobenzene which is the true arylating agent of the system owing to its higher reactivity in comparison to the bromobenzene.

The arylation of the nucleophiles catalyzed by the same catalyst or another one takes place and shifts the equilibrium by consuming the iodobenzene and regenerating the iodide.

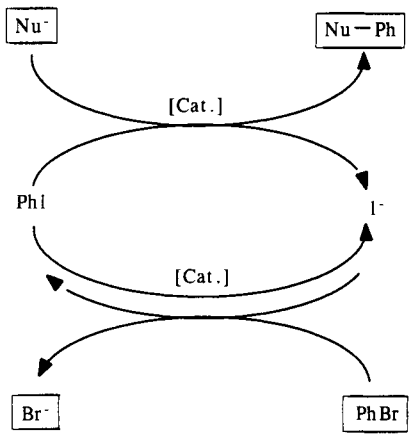


Fig. 22. Co-catalysis in the metal-catalyzed arylation of nucleophiles

In this way, the overall result is the arylation of the nucleophile by the bromobenzene with the enhanced reactivity of the iodobenzene.

We have tested this co-catalysis for the arylation of phosphines for example and have obtained an increase up to 50 % of the yields.

In the Figure 23 are summarized the different transformations, discussed before, of the bromoarenes into aromatic hydrocarbons, or more interestingly into arylamines, aryl ethers, phenols or iodoarenes.

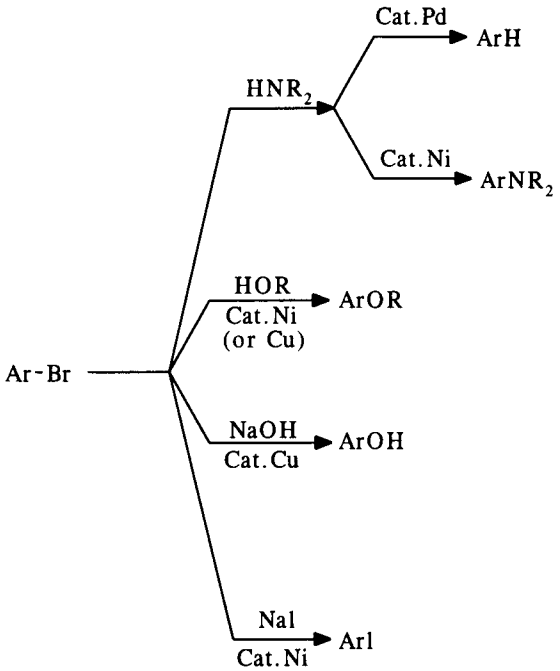


Fig. 23. Reactions of bromoarenes with hard (and soft) nucleophiles catalyzed by nickel, copper and palladium

All these transformations show :

- first, that the aryl bromides, by using metallic catalysts such as palladium, nickel or copper complexes can exhibit a diversified reactivity like their aliphatic analogs, the alkyl bromides;
- further, they show the pratical interest of such bromoarenes owing to the quantitative yields and very high selectivities reached in some cases of industrial interest.

Aknowledgements

The authors want to thanks Mr. S. Ratton who initiated the work and the co-workers who contributed to these investigations : Dr. Y. Beziat[1], Dr. D. Darwis[1], Dr. A. Nonn[2], Dr. J.L. Pirat[1], Dr. S. Rignol[1], Dr. R. Stammler[2].

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HYDROGEN BROMIDE ELIMINATION FROM DIASTEREOMERIC 3-BROMOFLAVANONES - MECHANISTIC ASPECTS

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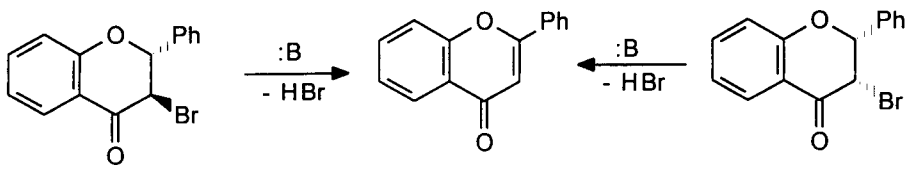
INTRODUCTION

In continuation of our studies on the chemistry of 3-halo- and 3-(alkane/arene)sulfonyloxyflavanones and -chromanones we decided to investigate the mechanism of hydrogen bromide elimination of diastereomeric 3-bromoflavanones. Dehydrohalogenation of 3-haloflavanones is well-known and widely used convenient method for the preparation of flavones, which takes place in the presence of various bases or heating, and occasionally, even in the course of halogenation of flavanones (refs. 1-5 and the references cited therein). However, no mechanistic studies have been published so far. In contrast with 3-haloflavanones, *trans*-3-(alkane/arene)sulfonyloxyflavanones were found to react in a more complex manner to give not only flavones but 2-arylidene-3-coumaranones (aurones) in the presence of O and N nucleophiles (refs. 6,7). In the hope to find a suitable model for this latter reaction we studied the dehydrobromination of *trans*- and *cis*-3-bromoflavanone **1** (Scheme 1) in detail. Our preliminary results and an evaluation using a simplified model has been reported (ref. 8) and a deeper insight is given in this communication.

Scheme 1.



1a **2** **1b**

EXPERIMENTAL

Trans-**1a** and *cis*-3-bromoflavanone **1b** were synthesized by the use of the v procedure of Bognár et al. (ref. 9). Cyclohexyl amine and N,N-dimethylformamide (DMF) was purified by distillation, potassium nitrate (Reanal) was used as received.

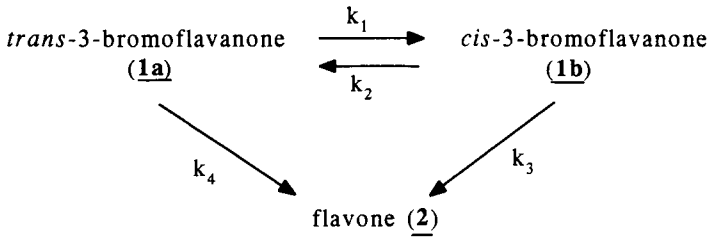
Kinetic measurements were performed on a Hitachi 150-20 UV/VIS spectrophotometer. Dehydrobrominations were studied in DMF solution using cyclohexyl amine (CHA) as the base. Applied CHA concentrations were 2, 2.5, 3, 3.5, 4 and $5*10^{-3}$ mole.dm^{-3}, initial concentration of **1** was $5*10^{-5}$ mole.dm^{-3} in every case (pseudo-first-order conditions). Ionic strength was adjusted to 10^{-1} mole.dm^{-3} with potassium nitrate. Kinetic curves / D(t) / were recorded at fix wavelength, λ = 290 nm and the temperature was maintained at 30, 35.5, 40°C. Stock solutions were made daily for **1a** and freshly for every measurement of **1b**. The reaction was started by injection of solution of **1** to the thermostated solution of CHA.

Kinetic curves were analyzed and the further correlations were determined with a nonlinear least-square-method PC program, working with the Gauss-Newton method.

^{1}H NMR spectra were taken from a Bruker WP 200 SY instrument in $CDCl_3$ solution using TMS as the internal standard.

ANALYSIS OF DATA

Based on the characteristic features of the three-component system investigated the following model may be used :



The shape of kinetic curves shown by Figure 1 clearly indicates the complexity of the reaction which requires at least five-parameter correlation (Eqn. 1).

$$D(t) = p_1 e^{p2t} + p_3 p4^t + p_5 \quad (1)$$

The integrated rate equations (refs. 10,11) for this model with the boundary conditions of **[1a]**=**[1a]**$_0$, **[1b]**=0 and [2]=0 at t=0 are

$$\mathbf{[1a]} = \frac{(k_1 + k_4 + m_2)[\underline{1a}]_0}{m_2 - m_1} e^{m1t} + \frac{(k_1 + k_4 + m_1)[\underline{1a}]_0}{m_2 - m_1} e^{m2t} \quad (2)$$

$$\mathbf{[1b]} = \frac{(k_1 + k_4 + m_2)(k_1 + k_4 + m_1)[\underline{1a}]_0}{(m_2 - m_1)k} (e^{m1t} - e^{m2t}) \quad (3)$$

where

$$m_1 = 1/2\left\{-(k_1 + k_2 + k_3 + k_4) - \left[(k_1 + k_2 + k_3 + k_4)^2 - 4(k_2k_4 + k_1k_3 + k_3k_4)\right]^{1/2}\right\}$$

$$m_2 = 1/2\left\{-(k_1 + k_2 + k_3 + k_4) + \left[(k_1 + k_2 + k_3 + k_4)^2 - 4(k_2k_4 + k_1k_3 + k_3k_4)\right]^{1/2}\right\}$$

Based on these integrated equations, the kinetic curve, i.e. the change of absorbance in time, can be written as follows :

$$D(t) = \left[\frac{A_0(k_1 + k_4 + p_4)(\varepsilon_1 - \varepsilon_3)}{p_4 - p_2} + \frac{A_0(k_1 + k_4 + p_2)(k_1 + k_4 + p_4)(\varepsilon_2 - \varepsilon_3)}{(p_4 - p_2)k_2}\right] * e^{p_2 t} -$$

$$-\left[\frac{A_0(k_1 + k_4 + p_2)(\varepsilon_1 - \varepsilon_3)}{p_4 - p_2} + \frac{A_0(k_1 + k_4 + p_2)(k_1 + k_4 + p_4)(\varepsilon_2 - \varepsilon_3)}{(p_4 - p_2)k_2}\right] * e^{p_2 t} + \varepsilon_3 A_0 \quad (4)$$

where A_0 is the initial concentration of **1a**, ε_1 is the molar absorption coefficient of **1a**, ε_2 is the molar absorption coefficient of **1b** and ε_3 is the molar absorption coefficient of flavone **2**, and

$$p_2 = 1/2\left\{-(k_1+k_2+k_3+k_4)-\left[(k_1+k_2+k_3+k_4)^2-4(k_2k_4+k_1k_3+k_3k_4)\right]^{1/2}\right\} \quad (5)$$

$$p_4 = 1/2\left\{-(k_1+k_2+k_3+k_4)+\left[(k_1+k_2+k_3+k_4)^2-4(k_2k_4+k_1k_3+k_3k_4)\right]^{1/2}\right\} \quad (6)$$

The kinetic curve of the reaction starting from *cis*-3-bromoflavanone (**1b**) may be derived similarly to give Equation 7.

$$D(t)=\frac{B_0}{p_2-p_4}\left[k_2(\varepsilon_1-\varepsilon_3)+(k_1+p_2)(\varepsilon_2-\varepsilon_3)\right]*e^{P_2t}-$$

$$-\frac{B_0}{p_2-p_4}\left[k_2(\varepsilon_1-\varepsilon_3)+(k_1+p_4)(\varepsilon_2-\varepsilon_3)\right]*e^{p4t}+\varepsilon_3B_0 \quad (7)$$

where B_0 is the initial concentration of **1b**, ε_1, ε_2, ε_3, p_2 and p_4 is the same as in Equations 4-6.

It means, an exact evaluation of both kinetic curves may be given using the five-parameter equation represented by Equation (1).

Since **1a** and **1b** are diastereomeric compounds differing only in their stereochemistry at C-3, $\varepsilon_1 \sim \varepsilon_2$ and ε_1, $\varepsilon_2 << \varepsilon_3$, thus we can consider $\varepsilon_1 \sim \varepsilon_2 \approx \varepsilon_2 - \varepsilon_3$. On the basis of this simplification, the p_3 parameter is

$$p_3=\frac{B_0}{p_2-p_4}\left[k_2(\varepsilon_1-\varepsilon_3)+(k_1+p_4)(\varepsilon_2-\varepsilon_3)\right]$$

and Equation (7) can be transform as

$$Z=\frac{-p_3(p_2-p_4)}{B_0(\varepsilon_1-\varepsilon_3)}-p_4 \approx k_1+k_2 \quad (8)$$

Starting from Equations (5) and (6) we can obtain that

$$p_2 * p_4 = k_2k_4 + k_1k_3 + k_3k_4 \quad (9)$$

and

$$-(p_2 + p)_4 = k_1 + k_2 + k_3 + k_4 \quad (10)$$

In accordance with the results reported previously (ref. 8), the different stability properties of the isomers and the model calculations using numeric ε_i and p_i parameters we can use the approximation of k_1, $k_3 >> k_4$, as well. Thus, Equations (9) and (10) can be rewritten in simplier forms

$$p_2 * p_4 \approx k_1k_3 \quad (11)$$

$$-(p_2 + p)_4 \approx k_1 + k_2 + k_3 \quad (12)$$

RESULTS AND DISCUSSION

Recorded kinetic curves were fitted to the five-parameter Equation (1). The parameters p_i with their errors and the standard deviation of regressions are summarized in Tables 1-6. Comparison of the data confirm the previously reported (refs. 8,12) similarity in the behavior of the two isomers in the presence of strong bases in spite of the different shape of the kinetic curves. The relatively good agreement of exponents p_2, p_4 computed for the diastereomers at the same temperature and amine concentration demonstrates the validity of the model used. From comparison of Equations (4) and (7) it follows that both reaction must give the same exponent.

Data given in Tables 1-6 clearly show a significant dependence of p_2 and p_4 on amine concentration, that is, at least one of the apparent rate constants k_i contains a concentration factor. Thus, according to the mathematical considerations outlined in the Analysis of Data Paragraph, both p_2, p_4 exponents and the derived variables $-(p_2 + p)_4$, $p_2 * p_4$ and Z (see Eqns. 8-12) are the combinations of the apparent rate constants (k_i). To characterize these dependences, derived variables $-(p_2+p)_4$, p_2*p_4 and Z (Eqns. 8,11 and 12) were correlated with the amine concentration using a non-linear regression program to find the best fit. Computation resulted in a linear dependence for $-(p_2 + p)_4$ and Z, that is

$$-(p_2 + p)_4 = a*[CHA] + b \quad (13)$$

and $Z = d * [CHA] + f \quad (14)$

and a quadratic dependence for $p_2 * p_4$, that is

$$p_2 * p_4 = c*[CHA]^2 \quad (15)$$

Parameters, errors and deviations are given in Tables 7-9 and one representative plot for every correlation is shown by Figures 2, 3 and 4. Moreover, data of Tables 7 and 8 indicates that both b and f is very small positive or negative number which equals to zero within the range of the experimental errors. To verify this assumption, fittings were repeated using linear regression without intercept (b, d=0)

$$-(p_2 + p)_4 = a_1 * [CHA] \quad (16)$$
$$Z = d_1 * [CHA] \quad (17)$$

and no significant difference was found between the two correlation on the basis of standard deviation.

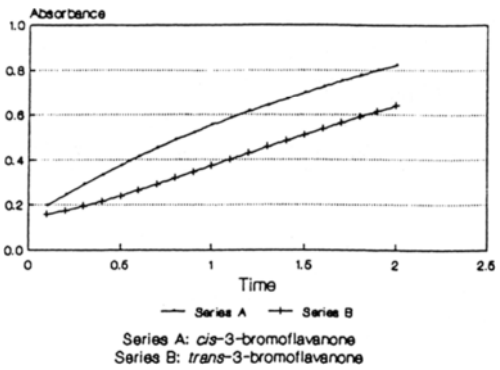


Fig. 1.Representative kinetic curves
[CHA]=2.5*10^{-3}, t=35.5°C

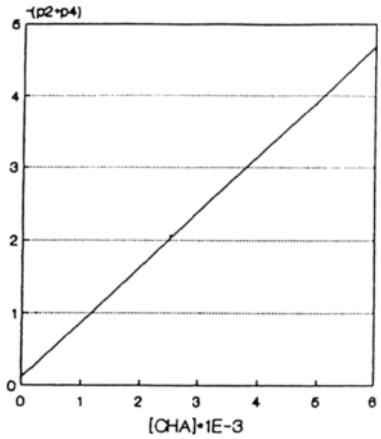


Fig. 2. -(p_2+p_4)vs. [CHA]
1a, t=35.5°C, N=6

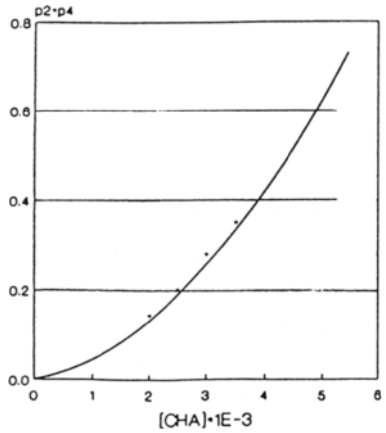


Fig. 3. p_2*p_4 vs. [CHA]
1a, t=35.5°C, N=6

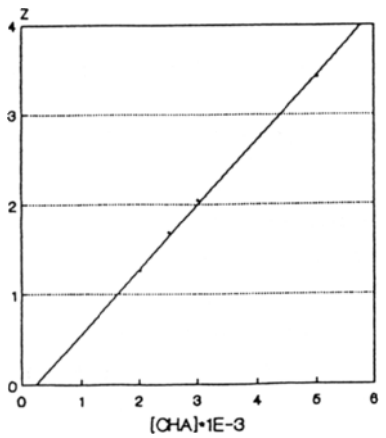


Fig. 4. Z vs. [CHA]
1a, t=30°C, N=6

Table 1. Exponents of five-parameter approximation of kinetic curves for *trans*-**1** (t=30°C)[a]

[CHA] $*10^{-3}$	p_1	$-p_2$	$-p_3$	$-p_4$	p_5	ASD $*10^{-4}$
2.0	.221±1*10^{-3}	1.18±.01	1.81±6*10^{-4}	.157±4*10^{-4}	1.66±2*10^{-3}	4.56
2.5	.177±1*10^{-3}	1.47±.02	1.67±4*10^{-4}	.182±4*10^{-4}	1.59±1*10^{-3}	5.69
3.0	.232±1*10^{-3}	1.77±.02	1.85±7*10^{-4}	.217±3*10^{-4}	1.69±9*10^{-4}	6.46
3.5	.214±1*10^{-3}	1.95±.02	1.79±7*10^{-4}	.230±3*10^{-4}	1.63±6*10^{-4}	5.43
4.0	.171±3*10^{-3}	1.93±.08	1.83±2*10^{-3}	.248±9*10^{-4}	1.69±2*10^{-3}	17.07
5.0	.214±.035	3.36±.78	1.94±9*10^{-3}	.299±4*10^{-3}	1.81±6*10^{-3}	105.10

[a] Number of measured points (N) = 95
ASD : Average standard deviation of regression

Table 2. Exponents of five-parameter approximation of kinetic curves for *trans*-**1** (t=35.5°C)[a]

[CHA] $*10^{-3}$	p_1	$-p_2$	$-p_3$	$-p_4$	p_5	ASD $*10^{-4}$
2.0	.211±1*10^{-3}	1.43±.02	1.71±9*10^{-4}	.210±4*10^{-4}	1.64±1*10^{-3}	5.64
2.5	.199±1*10^{-3}	1.91±.02	1.74±8*10^{-4}	.244±3*10^{-4}	1.68±6*10^{-4}	5.72
3.0	.199±2*10^{-3}	2.19±.03	1.76±1*10^{-3}	.266±4*10^{-4}	1.69±6*10^{-4}	7.70
3.5	.196±2*10^{-3}	2.43±.04	1.79±9*10^{-4}	.293±3*10^{-4}	1.71±5*10^{-4}	7.24
4.0	.219±3*10^{-3}	2.95±.06	1.84±1*10^{-3}	.357±5*10^{-4}	1.72±4*10^{-4}	9.92
5.0	.204±3*10^{-3}	3.72±.07	1.75±9*10^{-4}	.399±3*10^{-4}	1.63±2*10^{-4}	7.19

[a] Number of measured points (N) = 95
ASD : Average standard deviation of regression

Table 3. Exponents of five-parameter approximation of kinetic curves for *trans*-**1** (t=40°C)[a]

[CHA] $*10^{-3}$	p_1	$-p_2$	$-p_3$	$-p_4$	p_5	ASD $*10^{-4}$
2.0	.261±2*10^{-3}	1.49±.02	1.86±1*10^{-3}	.243±4*10^{-4}	1.75±8*10^{-4}	6.06
2.5	.249±1*10^{-3}	1.96±.02	1.84±1*10^{-3}	.296±3*10^{-4}	1.73±4*10^{-4}	5.94
3.0	.235±2*10^{-3}	2.30±.04	1.81±1*10^{-3}	.329±4*10^{-4}	1.70±4*10^{-4}	8.02
3.5	.246±3*10^{-3}	2.66±.05	1.88±1*10^{-3}	.353±4*10^{-4}	1.79±4*10^{-4}	7.92
4.0	.225±3*10^{-3}	3.49±.08	1.92±1*10^{-3}	.401±4*10^{-4}	1.81±3*10^{-4}	9.66
5.0	.230±3*10^{-3}	3.88±.07	1.89±1*10^{-3}	.465±4*10^{-4}	1.75±2*10^{-4}	7.26

[a] Number of measured points (N) = 95
ASD : Average standard deviation of regression

Table 4. Exponents of five-parameter approximation of kinetic curves for *cis*-**1** (t=30°C)[a]

[CHA] $*10^{-3}$	$-p_1$	$-p_2$	$-p_3$	$-p_4$	p_5	ASD $*10^{-4}$
2.0	.137±2*10^{-3}	1.01±.02	1.52±8*10^{-4}	.142±7*10^{-4}	1.75±3*10^{-3}	5.22
2.5	.114±1*10^{-3}	1.25±.02	1.51±6*10^{-4}	.161±5*10^{-4}	1.71±2*10^{-3}	5.22
3.0	.119±1*10^{-3}	1.50±.03	1.59±6*10^{-4}	.187±4*10^{-4}	1.79±1*10^{-3}	5.40
3.5	.101±1*10^{-3}	1.66±.04	1.44±8*10^{-4}	.212±5*10^{-4}	1.63±9*10^{-4}	6.40
4.0	.113±6*10^{-3}	1.62±.17	1.47±5*10^{-3}	.232±2*10^{-3}	1.66±4*10^{-3}	27.95
5.0	.112±1*10^{-3}	2.25±.05	1.49±9*10^{-4}	.303±4*10^{-4}	1.67±4*10^{-4}	5.93

[a] Number of measured points (N) = 95
ASD : Average standard deviation of regression

Table 5. Exponents of five-parameter approximation of kinetic curves for *cis*-**1** (t=35.5°C)v

[CHA] $*10^{-3}$	$-p_1$	$-p_2$	$-p_3$	$-p_4$	p_5	ASD $*10^{-4}$
2.0[a]	.144±2*10^{-3}	1.33±.02	1.50±1*10^{-3}	.227±5*10^{-4}	1.73±9*10^{-4}	5.80
2.5[b]	.105±1*10^{-3}	1.79±.04	1.49±1*10^{-3}	.265±4*10^{-4}	1.68±5*10^{-4}	5.91
3.0[c]	.100±1*10^{-3}	2.24±.06	1.44±1*10^{-3}	.314±4*10^{-4}	1.63±4*10^{-4}	6.49
3.5[d]	.107±2*10^{-3}	2.21±.07	1.52±2*10^{-3}	.364±5*10^{-4}	1.74±3*10^{-4}	7.21
4.0[e]	.080±2*10^{-3}	2.95±.12	1.56±1*10^{-3}	.375±4*10^{-4}	1.78±3*10^{-4}	6.92
5.0[c]	.080±3*10^{-3}	3.43±.17	1.60±1*10^{-3}	.439±4*10^{-4}	1.82±2*10^{-4}	7.40

[a] N=64 [b] N=44 [c] N=33 [d] N=36 [e] N=35
ASD : Average standard deviation of regression

Table 6. Exponents of five-parameter approximation of kinetic curves for *cis*-**1** (t=40°C)[v]

[CHA] $*10^{-3}$	$-p_1$	$-p_2$	$-p_3$	$-p_4$	p_5	ASD $*10^{-4}$
2.0[a]	.151±2*10^{-3}	1.67±.03	1.48±2*10^{-3}	.295±5*10^{-4}	1.71±5*10^{-4}	6.54
2.5[b]	.102±1*10^{-3}	2.30±.07	1.52±1*10^{-3}	.330±4*10^{-4}	1.70±4*10^{-4}	6.71
3.0[b]	.101±2*10^{-3}	2.65±.09	1.49±1*10^{-3}	.365±4*10^{-4}	1.67±3*10^{-4}	7.20
3.5[c]	.083±2*10^{-3}	2.89±.15	1.52±2*10^{-3}	.416±5*10^{-4}	1.69±3*10^{-4}	8.34
4.0[d]	.097±3*10^{-3}	3.83±.17	1.53±1*10^{-3}	.454±4*10^{-4}	1.70±2*10^{-4}	7.37
5.0[e]	.089±2*10^{-3}	3.14±.15	1.55±2*10^{-3}	.532±6*10^{-4}	1.74±2*10^{-4}	7.28

[a] N=64 [b] N=57 [c] N=53 [d] N=52 [e] N=60
ASD : Average standard deviation of regression

Table 7. Calculated parameter for equations $-(p_2+p_4) = a * [CHA] + b$ and $-(p_2+p_4) = a_1 * [CHA]$

Entry v	Compd.	T(°C)	N[a]	a	b	a_1	ASD
1	*trans*	30	6	-	-	700.5±120.3	.2905
2	*cis*	30	6	430.9±47.0	.32±.16	-	.1134
3			5[b]	459.7±13.9	.26±.04	-	.0320
4			6	-	-	518.4±16.6	.1415
5			5[b]	-	-	534.2±12.5	.0942
6	*trans*	35.5	6	810.1±36.6	.03±.13	-	.0885
7			6	-	-	819.0±9.4	.0797
8	*cis*		6	762.8±67.8	.11±.24	-	.1637
9			6	-	-	793.9±17.7	.1506
10	*trans*	40	6	903.4±76.7	-.03±.27	-	.1853
11			6	-	-	894.1±19.5	.1661
12	*cis*		6	636.5±199.5	1.02±.69	-	.4818
13			5[c]	1065.5±128.1	-.16±.39	-	.2026
14			6	-	-	918.9±62.9	.5356
15			5[c]	-	-	1016.2±26.1	.1800

a Number of fitted points
b Neglecting $4*10^{-3}$ mol.dm^{-3} amine concentration
c Neglecting $5*10^{-3}$ mol.dm^{-3} amine concentration

Comparing Equations (8), (11) and (12) with Equations (13), (14) and (15) it follows that

$$-(p_2+p)_4 = (k_1'+k_2'+k_3')*[CHA] \quad (18)$$

$$z = (k_1'+k_2')*[CHA] \quad (19)$$

and

$$p_2*p_4 = k'_1*k'_2 * [CHA]^2 \quad (20)$$

The chemical meaning of these mathematical equations is that the rate law is first order with respect to the amine base for each reaction (i.e. interconversion of **1a** and **1b** and hydrogen bromide elimination).

Table 8. Calculated parameters for equations $Z = d*[CHA] + f$ and $Z = d_1 * [CHA]$

Entry v	T(°C)	N[a]	d	f	d_1	ASD
1	30	6	340.2±52.0	.32±.18	-	.1256
2		5[b]	368.2±33.2	.27±.11	-	.0765
3		6	-	-	429.7±17.7	.1509
4		5[b]	-	-	445.2±15.2	.1143
5	35.5	6	722.3±63.0	-.18±.22	-	.1521
6		6	-	-	673.4±17.2	.1467
7	40	6	554.4±189.4	.77±.65	-	.4574
8		5[c]	957.6±129.3	-.34±.40	-	.2044
9		6	-	-	766.5±55.6	.4737
10		5[c]	-	-	850.3±28.6	.1974

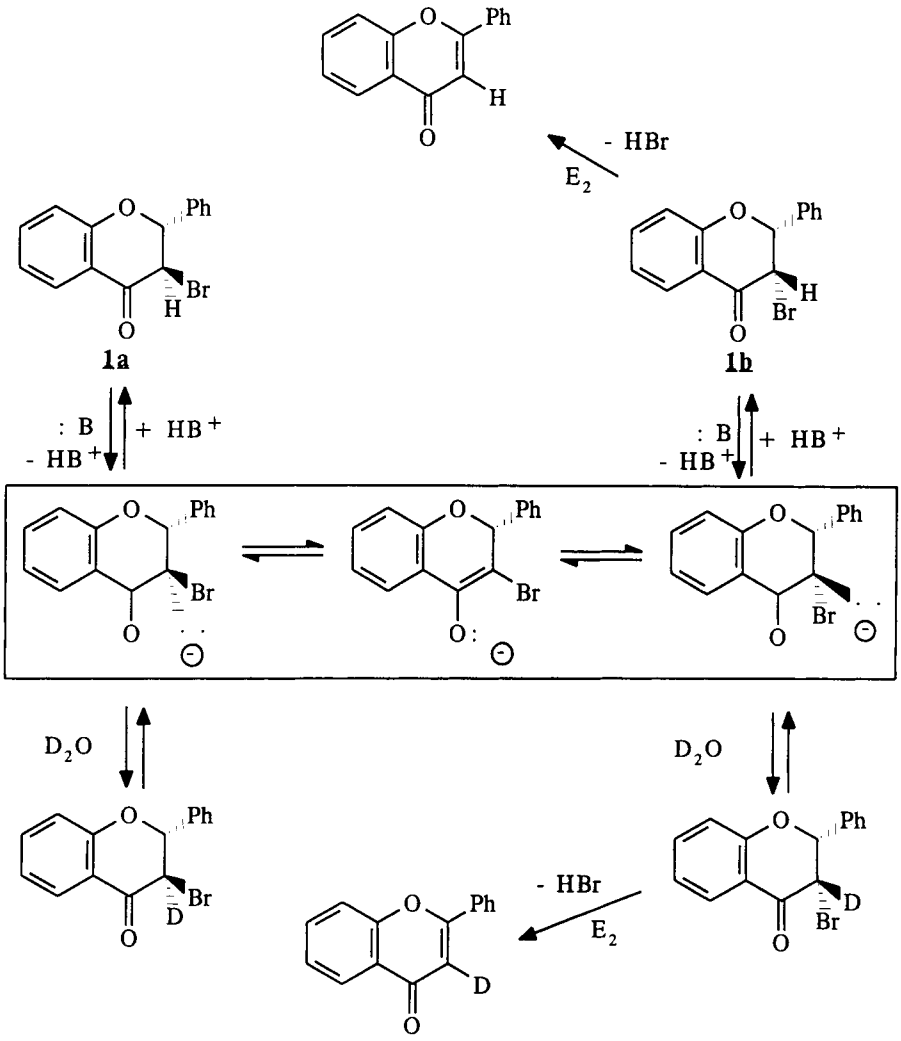
a Number of fitted points
b Neglecting $4*10^{-3}$ mol.dm^{-3} amine concentration
c Neglecting $5*10^{-3}$ mol.dm^{-3} amine concentration

Table 9. Calculated parameters for equations $p_2*p_4 = c * [CHA]^2$

Entry v	Compd.	T(°C)	N[a]	c	ASD
1	*trans*	30	6	37780±2010	.0687
2	*cis*		6	27134±1123	.0384
3			5[b]	28167±897	.0271
4	*trans*	35.5	6	61674±1836	.0627
5	*cis*		6	64810±2629	.0898
6	*trans*	40	6	77859±3180	.1086
7	*cis*		6	85456±9186	.3138
8			5[c]	106937±3413	.0795

a Number of fitted points
b Neglecting $4*10^{-3}$ mol.dm^{-3} amine concentration
c Neglecting $5*10^{-3}$ mol.dm^{-3} amine concentration

Scheme 2



The most plausible mechanism for the interconversion of **1a** and **1b** is shown in Scheme 2. Similar mechanism has been put forward for epimerization of α-substituted ketones under basic conditions and for the equilibration *via* an enolate prior to nucleophilic substitution was observed by Numazawa et al. (ref. 13). The same mechanism seems to operate in the reduction of some steroid α-haloketones (ref. 14) or *trans*-3-chloroflavanone (ref. 15) with sodium borohydride where an inversion of configuration takes place at the α carbon parallel to the reduction of the

carbonyl function. An equilibration has been reported between the C-2 epimers of 2-halo-3-methoxy-1,3-diphenylpropan-1-ones in the presence of isopropoxide ion (ref. 16). Deprotonation followed by enolization has also been demonstrated amongst α-sulfonyloxyketones (refs. 17,18).

The postulated mechanism shown by Scheme 2 was also supported by ^1H NMR measurements. In the presence of a weak base (such as pyridine-d_5) in DMSO-d_6-D_2O solution 65 % of **1a** remained unchanged after 3 days but a complete elimination leading to flavone (**2**) was observed in the case of **1b** and no considerable deuteration was found at C-3 atom of **2**.

The different reactivity mentioned above also proves the validity of inequality k_1, $k_3 >> k_4$ used in the simplification of our model. On the contrary, in the presence of CHA less than one equivalent the signals of both the **1a** and **1b** appear, a large extent of deuteration at C-3 is observed both in the *cis* and *trans* isomers and in the product flavone (**2**). Using an excess of amine both isomer gave **2** deuterated at C-3 to an extent ca. 80-85 %. Considering the kinetic profile of the interconversion we conclude that it takes place *via* an enolate where the rate determining step is the deprotonation at C-3.

The fact that the rate law of hydrogen bromide elimination is first order with respect to the base may be interpreted by an E2 mechanism. The antiperiplanar position of the hydrogen and the bromine atoms in **1b** also makes this mechanism very likely. Earlier the same mechanism was proposed for the elimination reaction of some tertiary α-halo ketones (ref. 19). Other mechanism, such as E1cB or E1, seems to be very improbable considering the lack of any deuteration at C-2 or the lack of any rearrangement and the fact that the generation of α-keto cations requires acidic conditions (ref. 20).

The values of the apparent rate constants k_i' for each temperature and the activation enthalpies calculated using the Eyring equation (ref. 21) are summarized in Table 10. However, these values of activation enthalpies are only approximative ones because of the applied simplification and the great range of experimental errors. Activation entropies were not calculated in the lack of absolute rate constants. Presuming the likely first order with respect to 3-bromoflavanones, as well, approximative activation entropies would be between -24 and -30 e.u. for **1a** → **1b** reaction, between -40 and - 45 e.u. for the **1b** → **1a** reaction and between -33 and -38 e.u. for the elimination step. These activation parameters are in accordance with the mechanisms proposed above.

Table 10. Apparent rate constants k_i' and approximative activation enthalpies

k'	T = 30°C	T = 35.5°C	T = 40°C	$\Delta H^{\ddagger}_{\ddagger}$ (kcal.mol^{-1})
k_1'	305.9[a]	537.8[a]	560.7[a]	11.1±4.9
	(316.5)[b]		(644.6)[b]	(13.0±2.9)
k_2'	123.8[a]	135.6[a]	205.8[a]	8.3±4.2
	(128.7)[b]		(205.7)[b]	(7.9±4.5)
k_3'	88.7[a]	120.5[a]	152.4[a]	9.6±0.1
	(89.0)[b]		(165.9)[b]	(11.1±1.0)

[a] Coefficients a_1, c and d_1 of **1b** computed for N=6 (see Tables 7-9) were used to calculate the apparent rate constants.
b Coefficients a_1 and d_1 of **1b** computed for N=5 (see Tables 7 and 8) and c of *cis*-**1** computed for N=6 (See Table 9) were used to calculate the apparent rate constants.

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BROMIDE-MEDIATED OXIDATIONS OF ORGANIC COMPOUNDS

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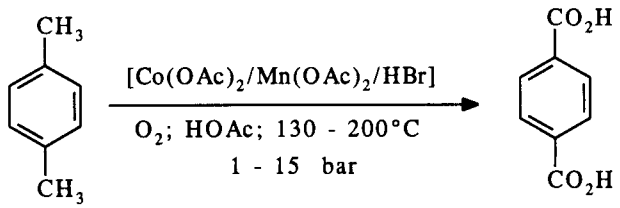
INTRODUCTION

In the late 1950's two groups - one at ICI (ref .1) and the other at the Mid-Century Corporation (ref. 2) - independently discovered that p-xylene is oxidized to terephthalic acid in almost quantitative yield when soluble bromides are used together with cobalt and manganese catalysts in acetic acid solvent at temperatures > 130 °C (ref. 3). This discovery formed the basis for what became known as the Mid-Century process and later, when the Mid-Century Corporation was acquired by Amoco, as the Amoco MC process for the commercial production of terephthalic acid. A large part of the ca. 6 million tons of the latter that are manufactured annually, on a worldwide basis, are produced via this method. This makes it the most important catalytic oxidation process (ref. 4).



(1)

In the absence of bromide ion the p-xylene undergoes rapid autoxidation to p-toluic acid but oxidation of the second methyl group is difficult, due to deactivation by the electron-withdrawing carboxyl group, and proceeds only in low yield at elevated temperatures. Although bromide-free processes were subsequently developed (ref. 5) they require the use of much higher amounts of cobalt catalyst and have not achieved the same importance as the Amoco-MC process. Indeed, the

latter can be considered as one of the most elegant and efficient of industrial processes. It proceeds in very high yield and virtually pure crystalline product is obtained by cooling the reaction mixture. The catalyst is then recycled as the mother liquor. Because of its extreme industrial importance a plethora of studies have been devoted to elucidating the mechanism of action of bromide ion in this system. The work of two groups is particularly noteworthy in this context. First, the group of Partenheimer at Amoco whose elegant mechanistic studies (refs. 7, 9) have played a decisive role in developing our current understanding of the process. Second, Partenheimer has often acknowledged his debt to the pioneering mechanistic studies of the group of Jones at ICI (refs. 10, 12). Much of the mechanistic discussion in the present paper (see later) is derived from the seminal studies of these two groups. Before delving into the mechanistic details, however, we shall first compare the relative merits of various methods for converting methylaromatic feedstocks to the corresponding aromatic carboxylic acids.

PRODUCTION METHODS FOR AROMATIC ACIDS

The various methods that are used for the production of aromatic acids from the corresponding substituted toluenes are outlined in Figure 1. The first two methods - chlorination/hydrolysis and nitric acid oxidation - have the disadvantage of relatively low atom utilization (ref .13) with the concomitant inorganic salt production. Catalytic autoxidation, in contrast, has an atom utilization of 87% (for Ar=Ph) and produces no inorganic salts and no chlorinated or nitrated byproducts. It consumes only the cheap raw material, oxygen, and produces water as the only byproduct.

$ArCH_3 \longrightarrow ArCO_2H$

1. CHLORINATION / HYDROLYSIS

$$ArCH_3 + 3\,Cl_2 \longrightarrow ArCCl_3 + 3\,HCl$$
$$ArCCl_3 + 2\,H_2O \longrightarrow ArCO_2H + 3\,HCl$$

ATOM UTILIZATION = 36 %

For Ar = C_6H_5

2. NITRIC ACID OXIDATION

$$ArCH_3 + 2\,HNO_3 \longrightarrow ArCO_2H + 2\,NO + 2\,H_2O$$

ATOM UTILIZATION = 56 %

3. CATALYTIC AUTOXIDATION

$$ArCH_3 + 1\ 1/2\ O_2 \xrightarrow{\text{catalyst}} ArCO_2H + H_2O$$

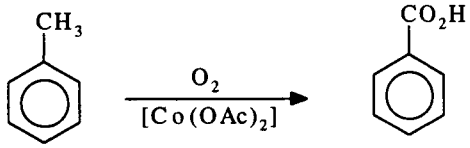
ATOM UTILIZATION = 87 %

* HIGH ATOM UTILIZATION
* LOW-SALT TECHNOLOGY
* NO CHLORO (NITRO) COMPOUNDS AS BYPRODUCTS
* CHEAP RAW MATERIAL (AIR)

Figure 1. Production of aromatic acids.

Consequently, as a result of increasing environmental pressure many chlorine and nitric acid based processes for the manufacture of substituted aromatic acids are currently being replaced by cleaner, catalytic autoxidation processes. Benzoic acid is traditionally manufactured (ref. 14) via cobalt-catalyzed autoxidation of toluene in the absence of solvent (Fig. 2). The selectivity is ca. 90% at 30% toluene conversion. As noted earlier, oxidation of p-xylene under these conditions gives p-toluic acid in high yield. For further oxidation to terephthalic acid the stronger bromide/cobalt/manganese cocktail is needed.

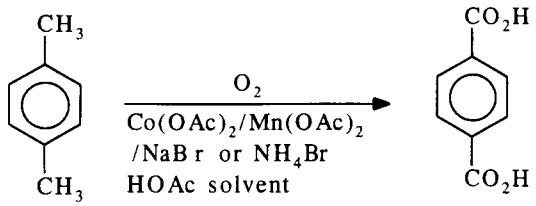
BENZOIC ACID



Temp : 165°C
Pressure : 10 bar

Conversion : ca. 30 %
Selectivity : 90 %

TEREPHTHALIC ACID (AMOCO/MC PROCESS)



Temp : 195°C
Pressure : 20 bar

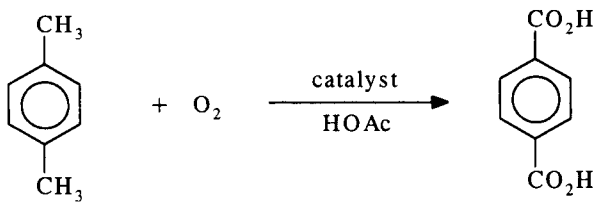
Conversion : > 95 %
Selectivity : > 95 %

Why Co + Mn + Br^- in HOAc ?

Figure 2. Industrial processes.

In Figure 3 the merits of the two processes for p-xylene oxidation are compared. The main disadvantages of the Eastman Kodak/Toray cooxidation method are the need for a cosubstrate (acetaldehyde of methylethylketone) with concomitant formation of a coproduct (0.21 ton of acetic acid per ton product) and high catalyst concentration. The Amoco MC process, on the other hand, has no coproduct and much lower catalyst concentrations but has the disadvantage that the bromide-containing reaction mixture is highly corrosive, necessitating the use of a titanium-lined reactor.

ca. 6 million tons per anum

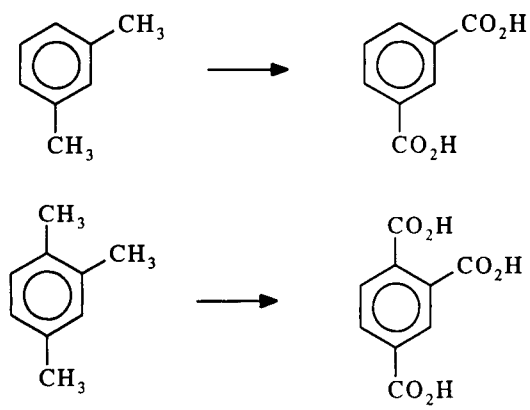


	COOXIDATION	BROMIDE-MEDIATED
	(Eastman-Kodak/Toray)	(Amoco/MC)
CATALYST	$Co(OAc)_2$	$Co(OAc)_2 + Mn(OAc)_2$
PROMOTOR	CH_3CHO (paraldehyde)	Br^-
TEMP. °C	100 - 140	195
PRESSURE (bar)	30	20
CONV./SEL. (%)	> 95 / > 95	> 95 / > 95
ADVANTAGE	LESS CORROSIVE	LOWER [CATALYST]
DISADVANTAGE	COPRODUCT HOAc	CORROSIVE
	(0.21 t/t)	(Ti-lined reactor)

Figure 3. Processes for terephthalic acid manufacture.

SCOPE OF THE AMOCO-MC PROCESS

Partenheimer has noted (ref. 15) that ca. 270 different substrates have been successfully oxidized using the Co/Mn/Br system. Some examples of aromatic di- and tricarboxylic acids that are commercially produced using the Amoco MC process are shown in Figure 4.



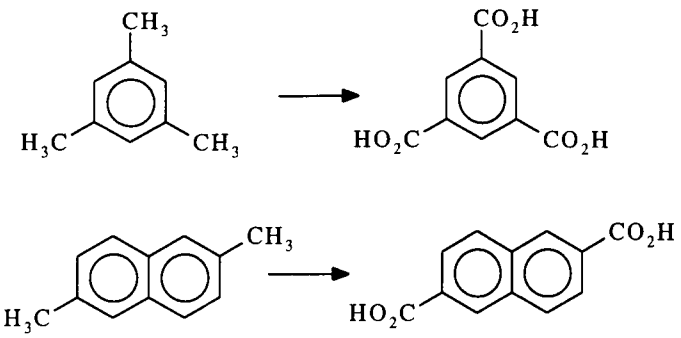
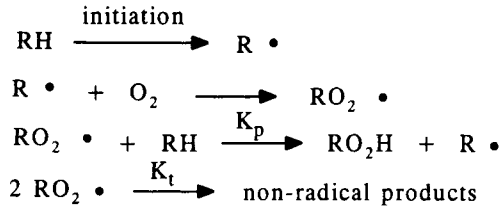


Figure 4. Acids produced by Amoco process.

A question which inevitably arises on surveying the enormous sucess of the Amoco catalyst is: why the combination Co/Mn/Br in acetic acid? In order to answer this question we must first examine the mechanism of free radical chain autoxidations of alkylaromatics (ref. 4).

MECHANISM OF HYDROCARBON AUTOXIDATION

The free radical chain mechanism of hydrocarbon autoxidation is outlined in Figure 5. The relative reactivities of different organic substrates towards dioxygen is determined by the relative rate constants of chain propagation (k_p) and chain termination (k_t) of the chain propagating alkylperoxy radicals, $RO_2\cdot$ The oxidizability of a substrate is defined as $k_p/(2k_t)^{1/2}$ and is an indication of how easily a particular substrate is autoxidized. It follows, therefore, that a low oxidizability can be a result of a low rate of propagation or a high rate of termination, or both. If one compares the oxidizabilities of toluene, ethylbenzene and cumene, for example, one sees that the substantial increase in relative oxidizability in the order toluene (1) < ethylbenzene (15) < cumene (107) is mainly due to the much higher rates of termination of the primary and secondary alkylperoxy radicals compared to tertiary alkylperoxy radicals (Fig. 5). The much higher oxidizability of benzaldehyde, on the other hand, is largely due to a much higher propagation rate.



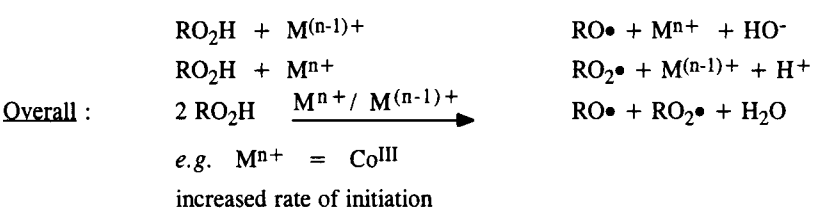
Substrate	$\frac{K_p}{(M^{-1}S^{-1})}$	$\frac{2k_t \times 10^{-6}}{(M^{-1}S^{-1})}$	$\frac{K_p/(2K_t)^{1/2} \times 10^3}{(M^{-1/2}S^{-1/2})}$	oxidizability	
$PhCH_3$ (a)	0.24	300	0.014	(1)	
$PhCH_2CH_3$ (a)	1.3	40	0.21	(15)	
$PhCH(CH_3)_2$ (a)	0.18	0.015	1.5	(107)	
PhCHO (b)	12000	1760	290	(21000)	

(a) Measured at 30°C (b) Measured at 0°C

Figure 5. Free radical autoxidation mechanism.

CATALYSIS BY METAL IONS

Variable valence transition metal ions, such as Co^{II}/Co^{III} and Mn^{II}/Mn^{III}, are able to catalyze hydrocarbon autoxidations by increasing the rate of chain initiation. Thus, redox reactions of the metal ions with alkyl hydroperoxides produce chain initiating alkoxy and alkylperoxy radicals (Fig. 6). Interestingly, aromatic percarboxylic acids, which are key intermediates in the oxidation of methylaromatics, were shown by Jones (ref. 10) to oxidize $Mn^{II}$and Co^{II}, to the corresponding μ-oxodimer of Mn^{III} or Co^{III}, via a heterolytic mechanism (Fig. 6).



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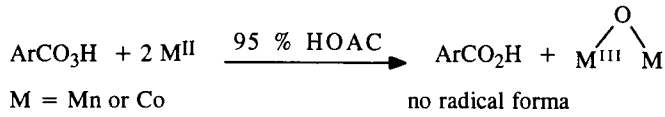
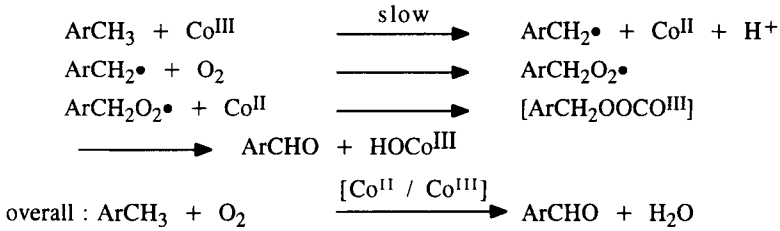


Figure 6. Catalysis by metal ions.

MECHANISM OF ALKYLAROMATIC OXIDATION

The metal-catalyzed autoxidation of substituted toluenes can be conveniently divided into two stages (Fig. 7). In the first stage the toluene undergoes cobalt-catalyzed autoxidation to the corresponding aromatic aldehyde. In the second stage the aldehyde undergoes rapid oxidation to the corresponding peracid which is subsequently reduced by cobalt(II) (or aldehyde) to give the final product, the aromatic carboxylic acid. The reactivity of the various molecules involved increases in the order $ArCH_3 < ArCH_2OH < ArCHO$.

STAGE 1 :



STAGE 2 :

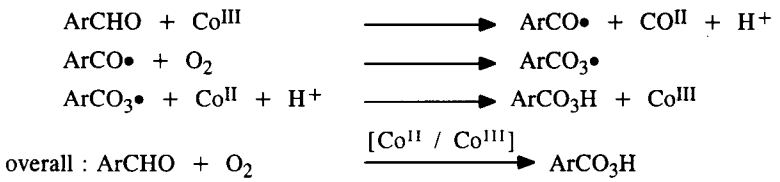
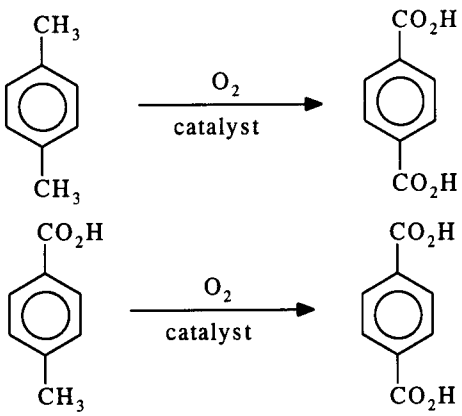


Figure 7. Mechanism of alkylaromatic oxidation.

In the oxidation of p-xylene the first methyl group undergoes rapid autoxidation to afford p-toluic acid (Fig. 8). The second methyl group is, however, deactivated by the electron-withdrawing carboxyl group, and further oxidation of p-toluic to terephthalic acid is much slower, i.e. the relative reactivities of toluene and p-toluic acid are 26:1 (Fig. 8). It is not surprising, therefore, that the autoxidation of p-xylene to terephthalic acid proved to be a difficult proposition.



$K_1 >> K_2$ (deactivating CO_2H group)

ArCH3	rel. rate
toluene	26
p-toluic acid	1

Figure 8. p-Xylene oxidation.

WHY COBALT/ACETIC ACID?

Partenheimer showed (ref. 15) that when toluene was subjected to dioxygen in acetic acid no reaction occurred, even at 205 °C and 27 bar. He also showed that when a solution of cobalt(II) acetate in acetic acid at 113 °C was treated with dioxygen ca. 1% of the cobalt was converted to the trivalent state. In the presence of a substituted toluene two reactions are possible: formation of a benzyl radical via one-electron oxidation of the substrate or decarboxylation of the acetate ligand (Fig. 9). Unfortunately, at the temperatures required for a reasonable rate of $ArCH_3$ oxidation (> 130 °C) competing decarboxylation predominates. As noted earlier, two methods have been devised to circumvent this undesirable

decarboxylation: addition of a cosubstrate (CH_3CHO or $CH_3COCH_2CH_3$) which allows for reaction at < 130 °C or the addition of bromide ion.

$$PhCH_3 + O_2 \xrightarrow[HOAc]{205\,^\circ C,\ 27\ bar} \text{no reaction}$$

$$Co^{II}(OAc)_2 + O_2 \xrightarrow[HOAc]{113\,^\circ C} \text{ca. 1 \% } Co^{III}$$

$$Co^{III}OAc \xrightarrow{ArCH_3} ArCH_2\bullet + Co^{II} + HOAc$$

$$Co^{III}OAc \longrightarrow CH_3\bullet + Co^{II} + CO_2$$

Temp. °C	$t_{1/2}$ $Co(OAc)_3$ in HOAc (min)
100	14
150	0.1

PROBLEM : > 130°C DECARBOXYLATION PREDOMINANT

SOLUTION : (a) CO-SUBSTRATE (CH_3CHO or MEK)
AT TEMP. < 130°C

or (b) ADD BROMIDE ION

Figure 9. Why cobalt/acetic acid?

WHY BROMIDE ION?

In the presence of bromide ion the slow one-electron transfer oxidation of the $ArCH_3$ substrate is replaced by the rapid one-electron oxidation of bromide ion by cobalt(III) to afford a bromine atom. The latter, or rather its adduct with bromide ion, Br_2 acts as the chain transfer agent in the reaction with the $ArCH_3$ substrate (Fig. 10).

$$Co^{III} + ArCH_3 \xrightarrow{\text{slow}} Co^{II} + ArCH_2\bullet + H^+$$

$$Co^{III} + Br^- \xrightarrow{\text{fast}} Co^{II} + Br\bullet$$

$$Br\bullet + Br^- \xrightarrow[\text{controlled}]{\text{diffusion}} Br_2^{\bullet -}$$

$$Br_2^{\bullet -} + ArCH_3 \longrightarrow ArCH_2\bullet + Br^- + HBr$$

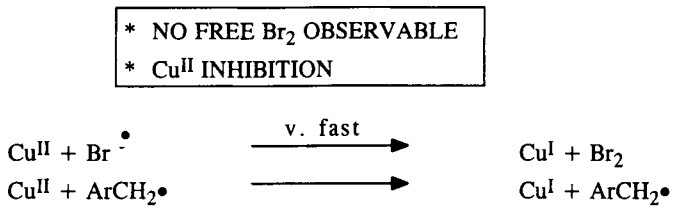


Figure 10. Why bromide ion?

As was noted by Jones (ref. 12) : the success of a metal bromide as a catalyst for alkylaromatic autoxidations depends on the ability of the metal to transfer rapidly and efficiently oxidizing power from various autoxidation intermediates onto bromide ion in a manner which generates Br·. The fact that no free bromine is observable in this system is consistent with rapid reaction of intermediate bromine atoms with the substrate. Inhibition of the reaction by cupric salts can be explained by the rapid removal of Br_2 or $ArCH_2$· via one-electron oxidation by Cu^{II} (Fig. 10).

REACTION OF $ArCO_3H$ WITH COBALT(II)

In order to provide an insight into the nature of the catalytic species Jones (refs. 11,12) studied the reaction of cobalt(II) acetate with m-chloroperbenzoic acid in 95% aqueous acetic acid at 0 °C. The composition of this reaction mixture corresponds reasonably well with that which is formed during $ArCH_3$ autoxidation. He found that $Co(OAc)_2$ was instantaneously oxidized to a μ-oxocobalt(III) dimer which was a very active catalyst and was denoted as Co^{IIIa} (Fig. 11). Within a few minutes at 25 °C this apple green complex reacted with a molecule of water to form a hydroxyl-bridged dimer which was olive green. This dimer, which was much less reactive, was denoted as Co^{IIIs}. On standing for several days at 25 °C the hydroxyl-bridged Co^{III} dimer reacted with Co^{II} to form a μ-oxo mixed trimer of Co^{III} and Co^{II}, denoted as Co^{IIIc}, which had previously been identified bij Ziolkowski and coworkers (ref. 16).

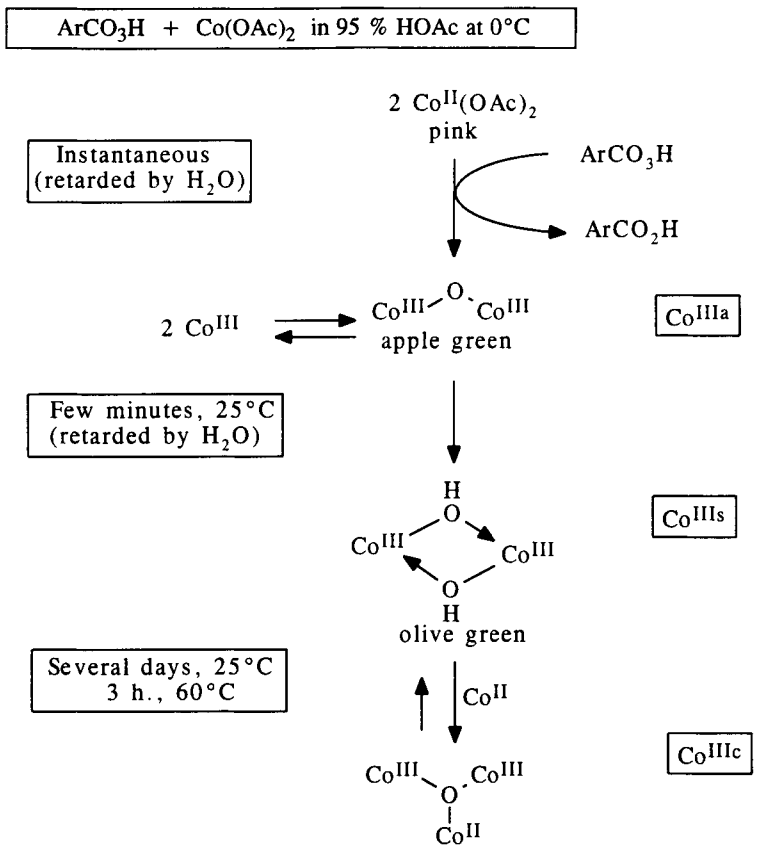


Figure 11. Reaction of $ArCO_3H$ with $Co(OAc)_2$ in HOAc.

The structures of the μ-oxo and the μ-dihydroxy dimer (refs. 17,18) are depicted in Figure 12.

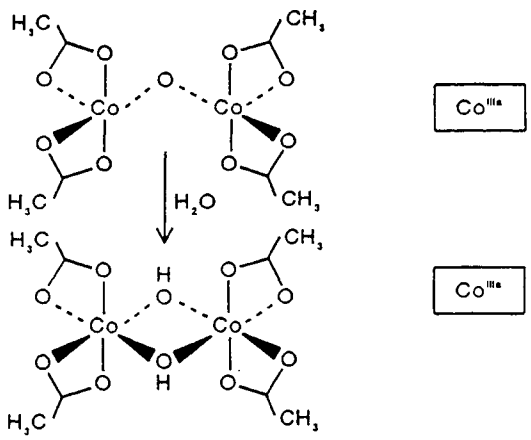


Figure 12. Structure of `cobalt(III) acetate'.

RELATIVE REACTIVITIES OF Co(III) SPECIES

Jones (refs. 11,12) subsequently investigated the relative reactivities of the various cobalt(III) species with Br^-, Mn^{II} and H_2O_2. The active μ-oxodimer, Co^{IIIa} was two to four orders of magnitude more reactive than Co^{IIIs} which was four to five times more reactive than Co^{IIIc} (Fig. 13). Furthermore, it should be noted that the rate of conversion of Co^{IIIa} to Co^{IIIs} is much higher than the rate of reaction of Co^{IIIa} with $ArCH_3$. In other words, in the absence of Br^- or Mn^{II} the cobalt species that reacts with $ArCH_3$ cannot be Co^{IIIa}.

	Co^{IIIa}		Co^{IIIs}		Co^{IIIc}
Br^-	30.000	:	4	:	1
Mn^{II}	6000	:	4	:	1
H_2O_2	700	:	5	:	1

N.B. $Co^{IIIa} \xrightarrow{K_1} Co^{IIIs}$

$PhCH_3 + Co^{IIIa} \xrightarrow{K_2} Co^{II} + PhCH_2\bullet$

$K_1 >> K_2$

Figure 13. Relative reactivities of Co^{III} species.

RELATIVE RATES OF REACTIONS OF $ArCO_3H$ IN 90% HOAc AT 25 °C

Figure 14 shows the relative rates of various reactions for the decomposition of $ArCO_3H$ in acetic acid at 25 °C. Thermal homolytic decompostion is negligible under these conditions. The relative rates of reaction of $ArCO_3H$ with Co^{II}, Br^- and Mn^{II} are 3900:4.7:1 (ref. 9), which is not what one would expect from the decreasing order of reduction potentials: $Br^- > Mn^{II} > Co^{II}$. What this means in practice is that in a mixture containing roughly equal amounts of Co^{II}, Mn^{II} and Br^- together with $ArCO_3H$ more than 99% of the latter will preferentially react with the Co^{II}. Similarly, replacement of 5% of Mn^{II} with Co^{II} resulted in a nine-fold increase in rate (ref. 9).

REACTION			REL RATE
$ArCO_3H + Co^{II}$	⟶	Co^{III}	3900
$ArCO_3H + Br^-$	⟶	BrO^-	4.7
$ArCO_3H + Mn^{II}$	⟶	Mn^{III}	1
$ArCO_3H$	⟶	$ArCO_2\bullet + \bullet OH$	10^{-4}

N.B. Reduction potentials : $Br^- > Mn^{II} > Co^{II}$

Figure 14. Relative rates of reactions of $ArCO_3H$ in 90% HOAc at 25 °C.

RELATIVE RATES OF REACTION OF Co^{IIIa}

Once the active Co^{IIIa} catalyst has been formed by peracid oxidation of Co^{II} the next step is determined by the relative rates of reaction of this species with other species present in the solution, i.e. Mn^{II}, Br^- and the substrate, and its rearrangement to the much less reactive Co^{IIIs}. As can be seen from these data (Fig. 15), the relative rates of reaction of Co^{IIIa} with Mn^{II}, Br^- and p-xylene are 940, 84 and 0.03, compared to 1 for the conversion of Co^{IIIa} to Co^{IIIs} (ref. 9). This means that in a mixture containing Co^{IIIa}, Mn^{II}, Br^- and p-xylene, > 90% of Co^{IIIa} reacts with Mn^{II} to afford Mn^{III} and that there is no reaction of Co^{IIIa} with the p-xylene substrate.

REACTION			TEMP. °C	REL. RATE
Co^{IIIa} + Mn^{II}	⟶	Mn^{III}	23	940
Co^{IIIa} + Br^-	⟶	$Br\bullet$	23	84
Co^{IIIa}	⟶	Co^{IIIa}	25	1
Co^{IIIa} + p-xylene	⟶	$ArCH_2\bullet$	80	0.03

Figure 15. Relative rates of reaction of Co^{IIIa} in 90% HOAc.

SYNERGISTIC EFFECT OF Mn/Co/Br$^-$

Based on the above analysis of the individual steps involved we are now able to provide an interpretation of the synergistic effect of Co/Mn/Br$^-$ in the Amoco system (Fig. 16). With cobalt alone in acetic acid the reaction of cobalt(III) with $ArCH_3$ (p-toluic acid) is much too slow. Bromide alone is rapidly oxidized by $ArCO_3H$, to afford BrO^- by a heterolytic mechanism. In the presence of cobalt, bromide ion is oxidized to chain-propagating bromine atoms. Unfortunately, one-electron oxidation of acetate ligands seriously competes with this process. In the presence of manganese and bromide the oxidation of Mn^{II} to Mn^{III} by $ArCO_3H$ is too slow. In contrast, in the presence of Co/Mn/Br$^-$ the Mn^{II} is rapidly oxidized by Co^{III} to give Mn^{III} which rapidly oxidizes Br$^-$ to Br·, The latter then reacts with the substrate to afford the $ArCH_2$· radical. Because Co^{III} is rapidly removed from the reaction mixture by reaction with Mn^{II} this means that there is a low steady-state concentration of Co^{III} and, hence, much less competing decarboxylation of acetic acid by Co^{III} (refs. 8,9).

1. COBALT ALONE

$Co^{III} + ArCH_3 \longrightarrow ArCH_2\bullet$ too slow

2. BROMIDE ALONE

$Br^- + ArCO_3H \longrightarrow BrO^-$ (no radicals)

$HBr + O_2 \not\longrightarrow Br\bullet + HO_2\bullet$

3. COBALT + BROMIDE

$Co^{III} \xrightarrow{Br^-} Co^{II} + Br\bullet$

$Co^{III} \xrightarrow{AcO^-} Co^{II} + CH_3\bullet + CO_2$

4. MANGANESE + BROMIDE

$Mn^{II} + ArCO_3H \longrightarrow Mn^{III}$ too slow

5. COBALT / MANGANESE / BROMIDE

$Co^{III} + Mn^{II} \xrightarrow{fast} Co^{II} + Mn^{II}$

$Mn^{III} + Br^- \xrightarrow{fast} Mn^{II} + Br\bullet$

* Low steady-state [Co^{III}]
* Less competing decarboxylation

REACTION			$t_{1/2}$ at 100°C (min.)	
$Co^{III}OAc$	⟶	$Co^{II} + CH_3\bullet + CO_2$	14	(56:1)
$Mn^{III}OAc$	⟶	$Mn^{II} + \bullet CH_2CO_2H$	790	
$Co^{III} + Mn^{II}$	⟶	Mn^{III}	< 0.2	
$Mn^{III} + Br^-$	⟶	$Mn^{II} + Br\bullet$	< 0.2	

Figure 16. Synergistic effect of $Mn/Co/Br^-$.

EFFECT OF Mn ON Co/Br^--CATALYZED AUTOXIDATIONS

The effects of manganese on the cobalt/bromide-catalyzed autoxidation of alkylaromatics are summarized in Figure 17. The use of the $Mn/Co/Br^-$ system allows for higher reaction temperatures and lower catalyst concentrations than the bromide-free processes. The only disavantage is the corrosive nature of the bromide-containing system which necessitates the use of titanium-lined reactors.

1. SYNERGISTIC INCREASE IN RATE
   100 % Co^{II} ⟶ 50 % Co^{II} + 50 % Mn^{II}
   4.3 x rate increase
   100 % Mn^{II} ⟶ 95 % Mn^{II} + 5 % Co^{II}
   9x rate increase
2. LESS OXIDATION OF HOAc SOLVENT
3. CATALYST CONCENTRATION CAN BE DECREASED
4. COST OF Mn ≈ 1 / 10x COST OF COBALT
5. HIGHER REACTION TEMPERATURE (190-210°C) AND LOWER CATALYST CONCENTRATION THAN WITH BROMIDE-FREE PROCESSES (< 140°C)
6. DISADVANTAGE : CORROSIVE NATURE OF BROMIDE

Figure 17. Effect of Mn on Co/Br^--catalyzed oxidations.

MECHANISM OF THE $Co/Mn/Br^-$ SYSTEM

The complete mechanism of the autoxidation of methylaromatics mediated by the Amoco, $Co/Mn/Br^-$ catalyst cocktail is depicted in Figure 18. The development of such a complex, elegant system must surely be considered a work of art.

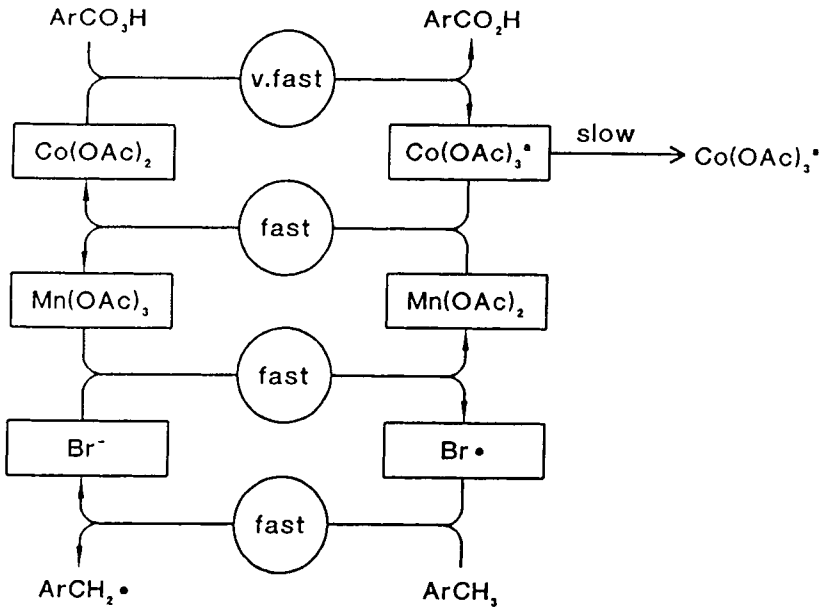
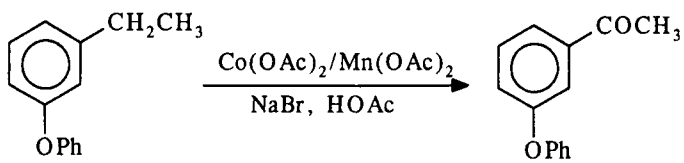


Figure 18. Mechanism of Co/Mn/Br^- system.

ALKYLBENZENE OXIDATION

As noted earlier, the Amoco catalyst system has been applied to the autoxidation of a wide variety of, mainly methylaromatic, substrates (ref. 19). It has also been applied to the oxidation of other alkylaromatics, e.g. the oxidation of m-phenoxyethylbenzene to the pharmaceutical intermediate, m-phenoxyacetophenone (2).



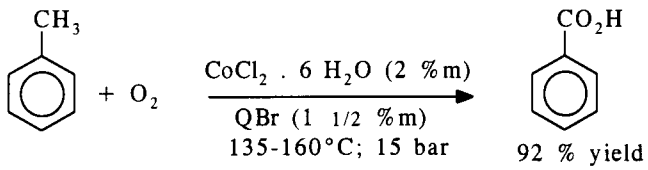
(2)

84 % yield
pharmaceutical intermediate

Co^{II} / Br^- / Mn^{II} (w/w) = 100 : 80 : 1

PHASE TRANSFER CATALYTIC SYSTEMS

Another catalytic system which has been successfully applied to the autoxidation of substituted toluenes involves the combination of Co/Br^- with a quaternary ammonium salt as a phase transfer catalyst (ref. 20). For example, cobalt(II) chloride in combination with certain tetraalkylammonium bromides or tetraalkylphosphonium bromides afforded benzoic acid in 92% yield from toluene at 135-160 °C and 15 bar (Fig. 19). It should be noted that this system does not require the use of acetic acid as solvent. The function of the phase transfer catalyst is presumably to solubilize the cobalt in the $ArCH_3$ solvent via the formation of $Q^+[CoBr]^-$.



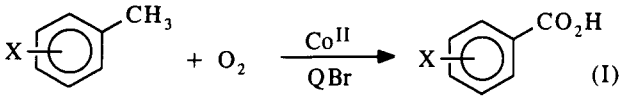
QBr = $(C_{10}H_{21})_2N(CH_3)_2Br$, $(C_6H_{13})_4NBr$, $(C_6H_{13})_4PBr$, etc.
$(C_4H_9)_4NBr$ infective

via : $QBr + Co^{II} \longrightarrow [Q]^+ [CoBr]^-$
soluble in $ArCH_3$

Figure 19. Phase transfer catalysis.

Similarly, Dakka and coworkers oxidized a variety of substituted toluenes to the corresponding carboxylic acids using a Co^{II}/QBr catalyst in combination with dioxygen at 137-170 °C (Table 1).

Table 1. Phase transfer catalysis in alkylaromatic oxidation.



X	Temp °C	QBr	(I) Yield (%)
p-chloro	137	$(C_6H_{13})_4NBr$	99
m-methyl	130	$(C_{10}H_{21})_2N(CH_3)_2Br$	97
o-methyl	135	$(C_8H_{17})_4NBr$	95
p-methyl	135	$(C_8H_{17})_4NBr$	96
p-nitro	170	$(C_6H_{13})_4NBr$	46
p-bromo	170	$(C_6H_{13})_4PBr$	~ 100
p-methoxy	140	$(C_6H_{13})_4NBr$	98
p-phenyl	140	$(C_{10}H_{21})_2N(CH_3)_2Br$	92
o-phenyl	140	$(C_{10}H_{21})_2N(CH_3)_2Br$	89

BROMIDE-MEDIATED AMMOXIDATION

In the presence of ammonium bromide cobalt (ref. 22) and manganese (ref. 23) have been shown to catalyze the ammoxidation of methylaromatics to the corresponding aromatic nitriles (Fig. 20). It is interesting to compare this homogeneous, liquid phase system with the more well-known vapour phase ammoxidation of alkylaromatics over oxidic catalysts (ref. 4).

$ArCH_3 \longrightarrow ArCO_2H$

1. CHLORINATION / HYDROLYSIS

$ArCH_3 + 3\,Cl_2 \longrightarrow ArCCl_3 + 3\,HCl$
$ArCCl_3 + 2\,H_2O \longrightarrow ArCO_2H + 3\,HCl$

ATOM UTILIZATION = 36 %

For Ar = C_6H_5

2. NITRIC ACID OXIDATION

$ArCH_3 + 2\,HNO_3 \longrightarrow ArCO_2H + 2\,NO + 2\,H_2O$

ATOM UTILIZATION = 56 %

3. CATALYTIC AUTOXIDATION

$$ArCH_3 + 1\ 1/2\ O_2 \xrightarrow{\text{catalyst}} ArCO_2H + H_2O$$

ATOM UTILIZATION = 87 %

* HIGH ATOM UTILIZATION
* LOW-SALT TECHNOLOGY
* NO CHLORO (NITRO) COMPOUNDS AS BYPRODUCTS
* CHEAP RAW MATERIAL (AIR)

Figure 20. Bromide-mediated ammoxidation.

AROMATIC ALDEHYDE PRODUCTION

All of the reactions discussed up till now involve the autoxidation of methylbenzenes to the corresponding carboxylic acids. From a practical viewpoint it would also be interesting to devise a process for the production of the corresponding aldehyde. Unfortunately, as noted earlier, the oxidizability of ArCHO is about four orders of magnitude higher than $ArCH_3$ which essentially precludes the selective production of the aldehyde when O_2 is the oxidant. With all other oxidants, on the other hand, the rate of oxidation of ArCHO is lower than that of $ArCH_3$ (ref. 24) (Fig. 21).

$$ArCH_3 \xrightarrow{K_1} ArCHO \xrightarrow{K_2} ArCO_2H$$

	Oxidizability	Ion. Potential (eV)
$PhCH_3$	1	8.8
PhCHO	ca. 10^4	9.5

WITH O_2 : $K_2 >> K_1$

WITH OTHER OXIDANTS : $K_1 >> K_2$

a. Stoichiometric oxidation e.g. Ce^{IV}, Mn^{IV}, Cr^{VI}

b. Electro(catalytic) oxidation

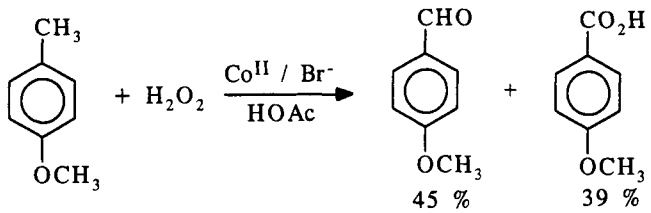
c. Catalytic oxygen transfer (Br- mediated)

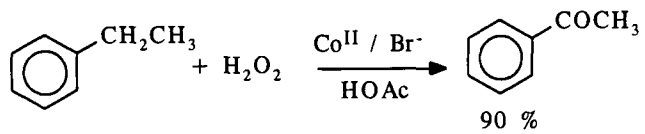
$$ArCH_3 + 2\ XO \rightarrow ArCHO + 2\ X + H_2O$$

XO = H_2O_2, RO_2H, etc.

Figure 21. Aromatic aldehyde production.

For example, oxidation of substituted toluenes with H_2O_2 in the presence of a Co^{II}/Br^- catalyst in acetic acid (ref. 25) resulted in the formation of substantial amounts of the corresponding aldehyde (Fig. 22).





MILD CONDITIONS; SHORT REACTION TIME

Figure 22. Side-chain oxidation with H_2O_2.

Similarly, Dakka and Sasson (ref. 26) showed that benzylic alcohols could be selectively oxidized to the corresponding aromatic aldehydes using HBr/H_2O_2 as the oxidant (Fig. 23). The reaction was not successful with electron-rich aromatics which underwent competing nuclear bromination.

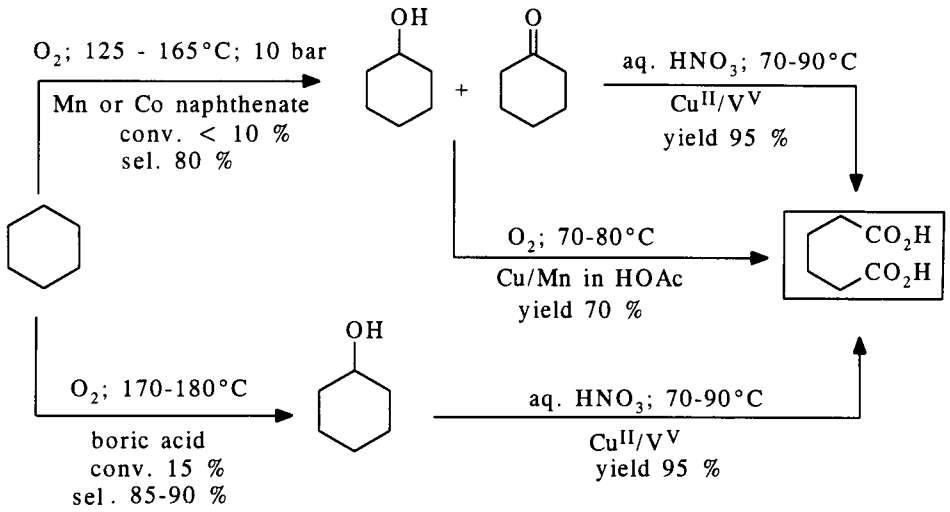
$$ArCH_2OH + H_2O_2 \xrightarrow[65\,^\circ C]{HBr\ (5\ \%m)} ArCHO + 2\ H_2O$$

Ar	Yield %
C_6H_5	84
4-$CH_3C_6H_4$	81
4-ClC_6H_4	87
4-BrC_6H_4	79

Figure 23. HBr-catalyzed oxidation with H_2O_2.

ADIPIC ACID PRODUCTION

Another reaction which enjoys much commercial interest is the production of adipic acid from cyclohexane oxidation. The two types of processes that are employed commercially are outlined in Figure 24.



PROBLEM : DECARBOXYLATION TO LOWER
MONO- AND DI-CARBOXYLIC ACIDS

30 kg C_6 RECYCLE + 0.25 BYPRODUCTS PER kg PRODUCT

Figure 24. Adipic acid production.

In one approach cyclohexane is autoxidized to a mixture of cyclohexanol and cyclohexanone in the presence of a Co or Mn naphthenate catalyst. This mixture is subsequently oxidized to adipic acid using nitric acid as the oxidant in the presence of a Cu^{II}/V^V catalyst. An alternative method using dioxygen in combination with Co or Mn in HOAc gives lower selectivities to adipic acid (70% vs 95%). Alternatively, autoxidation in the presence of stoichiometric amounts of boric acid produces cyclohexanol as the major product, which is subsequently oxidized to adipic acid using HNO_3 in the presence of Cu^{II}/V^V. The latter step produces substantial amounts of N_2O as a waste product.

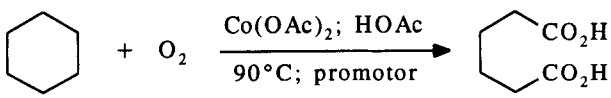
Obviously, there is a definite need for cleaner, more efficient routes to adipic acid. The question which immediately arises is, naturally, what does the Amoco system do in cyclohexane oxidation? In this context it is interesting to compare the relative oxidizabilities of toluene, cyclohexane, cyclohexanol and cyclohexanone (Table 2).

Table 2. Oxidizabilities of various substates.

Substrate	$\frac{K_p / (2K_t^{1/2}) \times 10^3}{(M^{-1/2}S^{-1/2})}$	rel. oxidizability
Toluene [a]	0.014	1
Cyclohexane [b]	0.23	16
Cyclohexanol [b]	0.4	29
Cyclohexanone [a]	0.5	36

(a) 30°C (b) 60°C

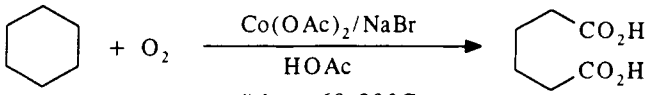
Interestingly, Tanaka (ref. 27) has reported the cooxidation of cyclohexane with acetaldehyde in the presence of a $Co(OAc)_2$ catalyst in acetic acid at 90 °C (3). Adipic acid was obtained in 73% selectivity at 88% cyclohexane conversion.



(3)

Promotor : CH_3CHO or cyclohexanol(one) conv. 88 %
sel. 73 %

Zaidi (ref. 28) has reported the autoxidation of cyclohexane in acetic acid, at 60-80 °C and 1 bar, in the presence of a $Co(OAc)_2$/NaBr catalyst (4). Adipic acid was obtained in 31% yield. Based on the results obtained in alkylaromatic oxidations it would be interesting to try the Co/Mn/Br^-/HOAc system in cyclohexane oxidation. It is, however, difficult to believe that this has not already been done.



(4)

$[Co(OAc)_2] = 7 \times 10^{-3}$ M

$[NaBr] = 4 \times 10^{-2}$ M

BROMIDE-CATALYZED OXIDATION WITH NaOCl

The examples quoted up till now have all involved the use of O_2 or H_2O_2 as the primary oxidant. In our last example we present the use of bromide ion as a catalyst in oxidations with sodium hypochlorite. Thus, bromide was shown to catalyze the oxidation of starch or inulin with NaOCl at pH = 10 (Fig. 25). This can be explained by assuming that the rate determining step involves cleavage of a C-C bond with concomitant loss of halide as the leaving group. Since Br^- is a much better leaving group than Cl^- cleavage via the alkyl bromite will be much more favourable (Fig. 25).

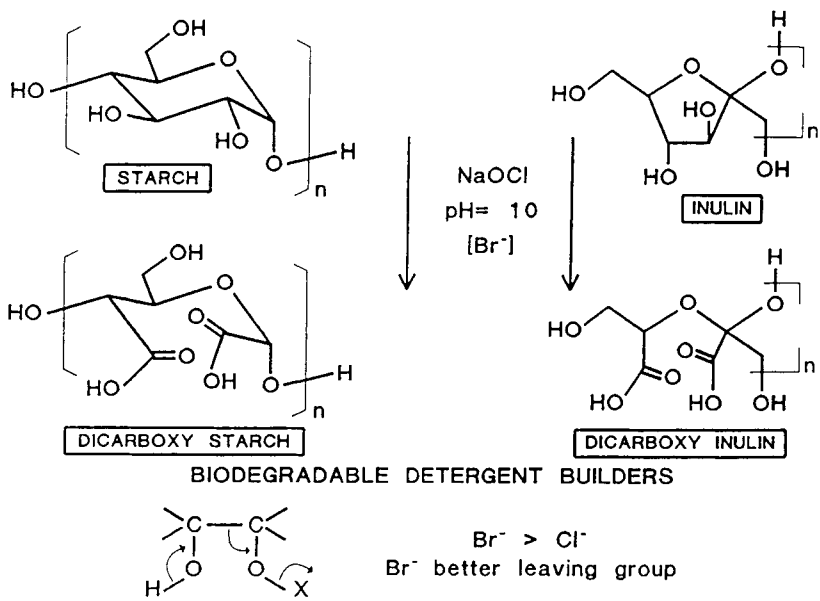


Figure 25. Bromide-catalyzed oxidation with NaOCl.

CONCLUDING REMARKS

The beauty of bromide-mediated oxidations is that they combine mechanistic complexity with practical simplicity and, hence, utility. They involve an intricate array of electron transfer steps in which bromine atoms function as go-betweens in transfering the oxidizing power of peroxidic intermediates, via redox metal ions, to the substrate. Because the finer mechanistic details of these elegant processes have often not been fully appreciated we feel that their full synthetic potential has not yet been realized. Hence, we envision further practical applications in the future.

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NEW CATALYTIC PROCESS FOR BROMINE RECOVERY

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INTRODUCTION

Waste HBr is a common byproduct of organic brominations. Frequently, this waste is neutralized with caustic, the resulting sodium bromide salt is discharged, and valuable bromine is lost. The economic advantages of recovery and recycle of this HBr have long been recognized (refs. 1, 3). In practice, recovery typically takes the form of conversion of the HBr to clear drilling fluids or alkylbromides (ref. 4) as shown in equations 1 and 2.

$$2\ HBr + Ca(OH)_2 \longrightarrow CaBr_2 + 2\ H_2O \quad (1)$$

$$HBr + CH_3OH \longrightarrow CH_3Br + H_2O \quad (2)$$

Recycle traditionally involves caustic scrubbing the gaseous HBr from bromination reactions (eqn. 3). The resulting sodium bromide solution is then treated with chlorine gas to generate bromine (eqn. 4).

$$HBr + NaOH \longrightarrow NaBr + H_2O \quad (3)$$

$$2\ NaBr + Cl_2 \longrightarrow Br_2 + 2\ NaCl \quad (4)$$

The resulting NaCl is then either deep-welled or discharged.

All of the methods of recovery and recycle have been limited by market forces. However, the importance of environmental issues in the selection of the HBr conversion or recycle processes has only more recently been recognized (refs. 5, 6). For example, proposed restrictions (refs. 7, 8) on methyl bromide manufacture could eliminate this high-volume, economical route to HBr conversion.

Similarly, increasing restrictions on discharge and deep welling could significantly reduce their potential for cost-effective waste handling.

Catalytic oxidation of waste HBr offers a more environmentally friendly recycle alternative than oxidation with chlorine, since catalytic oxidation yields byproduct water (eqn. 5) rather than salt requiring disposal or deep welling.

$$4\ HBr\ +\ O_2 \longrightarrow 2\ Br_2\ +\ 2\ H_2O \qquad (5)$$

This can lead to a 20-fold reduction in the effluent from the bromine recycle operation (ref. 4). An effective catalytic HBr oxidation process eluded researchers for almost 50 years (ref. 1). Although a wide range of catalysts were tested (refs. 1,2,9-16), they did not exhibit the combination of high activity and good stability required for a commercial process. Futhermore, the lack of effective heat management in previous work decreased the catalyst stability by causing severe local hot spots within the catalyst bed. These high temperatures caused promoter migration, leading to rapid catalyst deactivation.[11-13] We have recently developed a stable, high activity catalyst for the conversion of HBr to bromine using oxygen or air as the oxidant.[4,17] The catalyst is also highly resistant to deactivation by a broad range of contaminants commonly found in waste HBr streams.

NEW CATALYTIC PROCESS

The problem of heat management for this highly exothermic oxidation reaction was generally not recognized in the prior art literature. As a result, anhydrous HBr was typically fed to the catalyst bed (refs. 11, 13). Under these conditions, the adiabatic temperature rise is approximately 2000°C. The heat flux required to remove this high heat of reaction is too great for standard equipment. Futhermore, the materials of construction are not available to handle the resulting high-temperature corrosive environment. The catalytic oxidation process developed at Catalytica overcomes the heat management problem by using aqueous instead of anhydrous HBr. The use of 48 % aqueous HBr reduces the adiabatic temperature rise to only about 320°C. This allows the use of conventional heat removal methods such as a multitubular shell and tube heat exchanger-type reactor. The catalyst is packed in the tubes, and a heat transfer fluid is passed through the shell side to control the temperature. Commercially available alloys can then be used for tube construction.

A pilot unit was built to confirm effective heat control and to establish long-term catalyst stability (Fig. 1) (ref. 17). The pilot unit was designed around a single tube

of the same dimensions (2.54-cm diameter, 4-m length) and materials that would be used in a commercial scale reactor that could contain several hundred to several thousand such tubes.

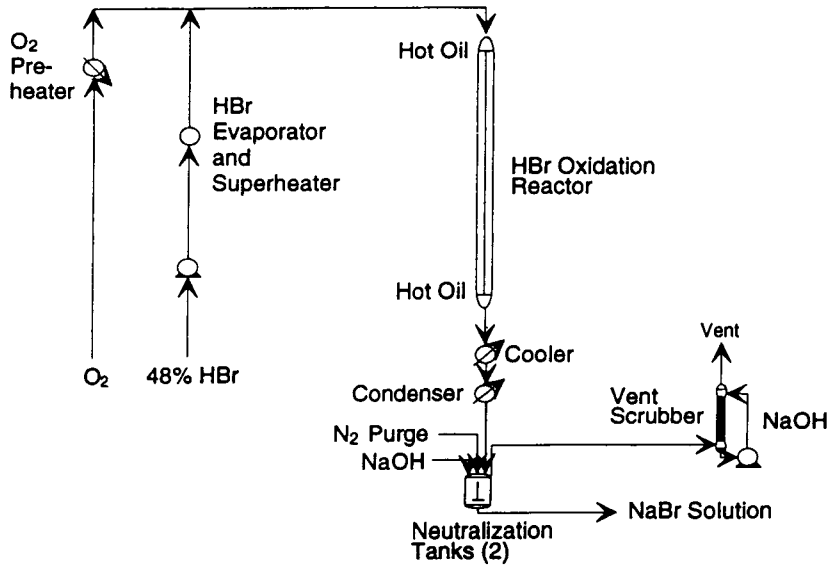

Fig. 1. Schematic of the pilot unit used for catalyst life and heat management testing.

The reactor was packed with 2.30 kg of 3-mm diameter extruded catalyst particles. The composition of the commercial waste HBr feed used in this study is given in Table 1.

Table 1. Composition of the aqueous HBr feed used for pilot unit testing

HBr	47.69 wt %
Density	1.4965 g/ml
Boiling point	126°C (approximate)
Free bromine	57 ppm
Organic contaminants	< 100 ppm
Inorganic chloride	0.02 wt %
Sulfate	6.7 ppm
Sodium	1.2 ppm

Using a hot oil system for heat transfer, the maximum temperature rise observed within the reactor at 98-99 % HBr conversion was only about 13°C at a reactor

inlet temperature of 275°C. This high conversion level was maintained under standard operating conditions during the 600-hour test period (Figure 2).

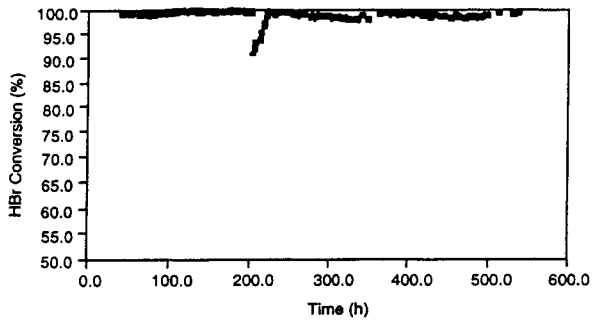

Fig.2. HBr conversion during catalyst life testing in single full-scale reactor tube showing high conversion throughout the test. The brief time at lower conversion was due to a unit upset.

The stability of the catalyst was demonstrated by constant position of the temperature maximum. The exotherm remained at the top of the catalyst bed and stayed at 13 ± 1°C during the 600-hour run.

The results of the pilot study were used to design a commercial process. The schematic for this process is shown in Figure 3.

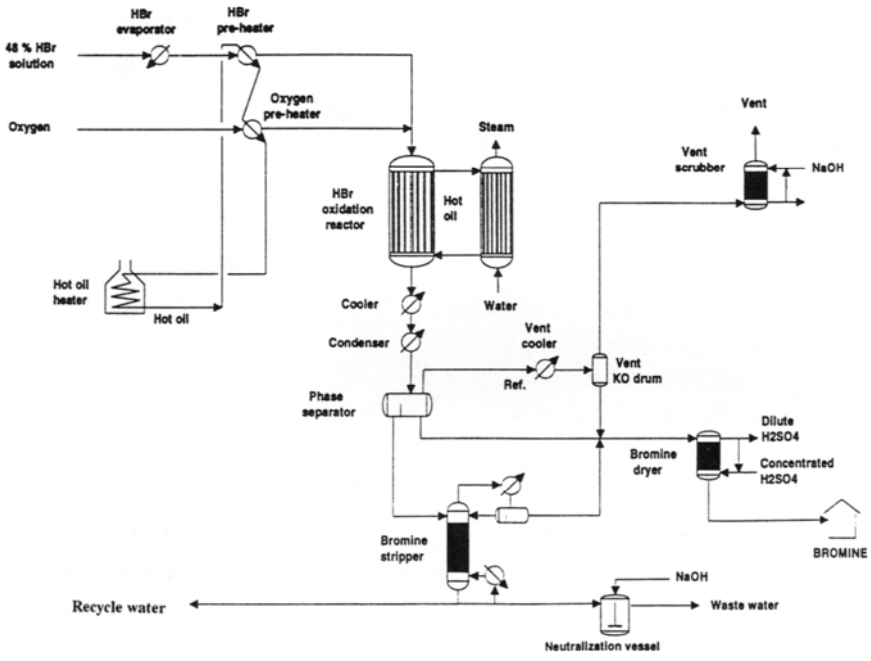

Fig. 3. Schematic of commercial catalytic HBr oxidation process.

The aqueous HBr is vaporized and superheated to the reactor inlet temperature (275-325°C), and then mixed with oxygen before entering the multitubular reactor. In the reactor, the HBr reacts with oxygen over the heterogeneous catalyst to produce bromine and water. The reactor effluent is then cooled and condensed. The bromine separation and purification is conducted according to conventional bromine industry practice. The bromine is separated from the water in a phase separator and dried using sulfuric acid. The water phase is stripped of bromine before discharge.

If a large volume of gaseous HBr is available from the upstream bromination process, it may be fed directly to the preheater. In this case, steam is cofed to the reactor to provide temperature control. This simplifies the process design by eliminating the vaporizer.

HBr CONTAMINANT STUDIES

One of the key challenges for this process is dealing with the wide range of contaminants in the waste HBr stream. Both inorganic and organic contaminants may be present. These contaminants are typically reactants and products of the upstream bromination process which generated the waste HBr. In addition, they may include corrosion products of upstream equipment or ionic materials present in the water used to scrub the gaseous bromination process effluent. The main concerns about contaminants in the feed streams are their effect on catalyst activity and stability and their effect on bromine product quality.

Two types of laboratory tests were conducted to evaluate contaminant tests, a catalyst stability test and a high-conversion bromine product test. For catalyst stability testing, only a small amount of catalyst was used (1.5 g) to ensure incomplete conversion of the HBr. If a feed contaminant causes catalyst deactivation, it is apparent as an immediate decrease in conversion. If an excess of catalyst was used instead, even if deactivation occurred at the inlet of the bed, it may not be detected until the region of deactivation moves considerably downstream. This could take many hours or days.

The high conversion test is operated to ensure that essentially complete conversion of the HBr is possible, and to study the fate of the feed contaminants. In this test, the conditions are selected to ensure complete conversion of the HBr. Several reaction pathways are then available to feed contaminants. They may undergo combustion, react with HBr, or react with the bromine formed. The extent of reaction via any of these pathways will depend on the nature of the contaminants and the temperature. Information concerning the fate of the contaminants can then be gained by analyzing the gas, bromine, and aqueous phases exiting the reactor.

Complete combustion of organic contaminants to CO_2 and water would be highly desirable. However, the same flame retarding properties which give many organic bromides their commercial value make their complete combustion difficult. In those cases, minimization of byproduct formation in the catalytic reactor and ease of separation of the organics from the bromine are desired. Since most commercial waste streams contain some level of contamination, it is important to gain an understanding of contaminant effects and fate in this catalytic process. Characterization of these contaminant effects is the focus of this paper.

Test Procedure

a. Laboratory-scale reactor. Our studies of contaminants have been conducted primarily in a laboratory-scale test unit. The laboratory-scale test unit is shown schematically in Figure 4.

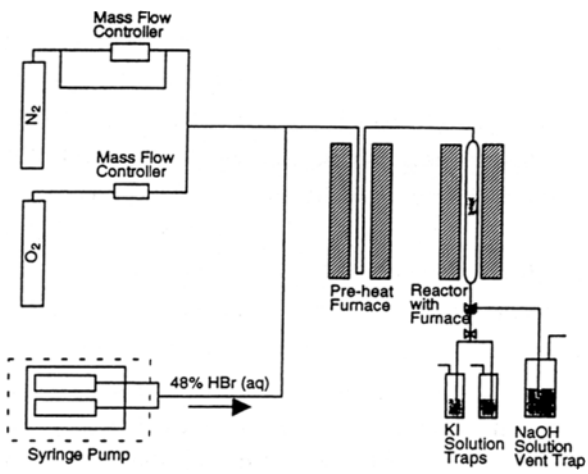

Fig. 4. Schematic of laboratory-scale test unit used for HBr feed contaminant studies.

The reactor is an 8-mm i.d. quartz tube located in a tube furnace. The quartz tube is packed with 20 by 30 mesh catalyst particles. The catalyst bed is positioned in the tube using quartz wool above and below the bed, with quartz chips filling the remainder of the reactor. The furnace temperature is controlled by a thermocouple inserted into the reactor tube and positioned about 3 mm above the catalyst bed. This allows operation at constant feed temperature into the reactor.

The oxygen feed to the reactor is controlled using Brooks 5850E Series mass flow controllers. Aqueous HBr is delivered to the reactor system using Harvard

Apparatus 22 syringue pump at a delivery rate of 6.0 cc/h. The effluent of the reactor passes through traps containing aqueous 4 M KI to collect HBr and Br_2. Conversion is measured by then titrating with sodium thiosulfate to determine the bromine content, and then with NaOH to determine the HBr content (ref. 4).

b. Model contaminated HBr streams. Model contaminants that represent classes of contaminants frequently encountered in waste HBr streams were tested. These include propionic acid, dibromoethane, dibromoethene, dichloroethane, dichloroethene, phenol, fluorobenzene, and HCl. These model contaminants were added to reagent grade 48 % aqueous HBr. The mixture was then fed to the vaporizer by syringe pump. The only exception was with fluorobenzene, where the solubility of fluorobenzene in aqueous HBr is too low to make this practical. In that case, the fluorobenzene was added to the reactor using a small oxygen stream saturated with fluorobenzene. The contaminants tested and their concentrations are given in Table 2.

Table 2. Model HBr feed contaminants and effects

Contaminant effect	Conc. (wt %)	Temp (°C)	
Propionic Acid	0.7	292	Deactivation
	0.7	320	None
Dibromoethane	0.6	300	None
Dibromoethene	0.6	300	None
Dichloroethane	0.6	300	None
Dichloroethene	1.0	300	None
Phenol	0.6	300	None
Fluorobenzene	1.5	300	None
HCl	5.0	300	None

c. Catalyst stability studies. In these studies. the reactor was charged with 1.5 g of 20-30 mesh catalyst particles blended with an equal volume of 18-35 mesh quartz chips. The aqueous HBr feed rate was 6.0 ml/hr. The oxygen feed rate was adjusted

to allow sufficient oxygen to convert all of the HBr to bromine and to combust all of the organic contaminant to CO_2 and H_2O. Conversion is measured as described earlier. The feed inlet temperature was 300±1°C to achieve a conversion target between 80 and 95 %. This partial conversion ensures that deactivation could be readily observed if it occurred. Corrosion coupons were placed downstream of the reactor to test contaminant effects.

d. High-conversion bromine quality studies. In these studies, the reactor was charged with 7.0 g of 20-30 mesh catalyst particles. The aqueous HBr feed rate was 6.0 ml/hr; the oxygen feed rate was adjusted to allow complete combustion of the organic contaminants and complete conversion of HBr. Studies were conducted at inlet temperature of 300°C and 335°C. Conversion was measured as described above, and product samples for organic analysis were trapped using an ice bath. Combustion of the organics was monitored by analyzing the effluent gas using a Hewlett Packard 5880A Series Gas Chromatograph equipped with a Hayesep D column. The quality of the dried, phase-separated bromine was analyzed by FT-IR (Bio-Rad FTS-40) (ref. 18) and NMR (Bruker MSL 400, 400 mHz, 9.4 Tesla). The aqueous phase was analyzed by extraction of organics using acetonitrile, followed by GC/mass spectrometry of the extracted material using a Hewlett-Packard 5988A GC/MS System.

HCl Contaminant Effects

The most commonly encountered inorganic contaminants in waste HBr streams are primarily low level bromide salts such as sodium bromide or calcium bromide. These do not provide a significant challenge to catalytic performance because they are unlikely to enter the catalytic reactor in significant quantities. Instead, the low operating temperature (about 128°C) of the vaporizer would cause them to be retained and concentrated in that vessel.

An inorganic contaminant that is relatively common in waste HBr streams and can be volatilized by the vaporizer is HCl. Separate studies (ref. 19) with the HBr oxidation catalyst have shown that conversion of HCl to chlorine is possible, but high conversion requires temperature near 400°C. In the presence of HBr, any chlorine produced by oxidation of HCl will oxidize the HBr to bromine (eqn. 6).

$$Cl_2 + 2\,HBr \longrightarrow 2\,HCl + Br_2 \qquad (6)$$

Therefore, if HCl is present as a contaminant, operation at less than full HBr conversion would be desired to ensure that all chlorine exits the reactor as HCl and is present in the aqueous phase rather than the bromine phase. If complete conversion were required, chlorine could readily be separated from bromine by distillation.

The effect of HCl on catalyst stability was tested using an aqueous HBr stream containing 5 % HCl. No decrease in conversion occurred during 24 hours on stream with a 300°C inlet temperature (Fig. 5).

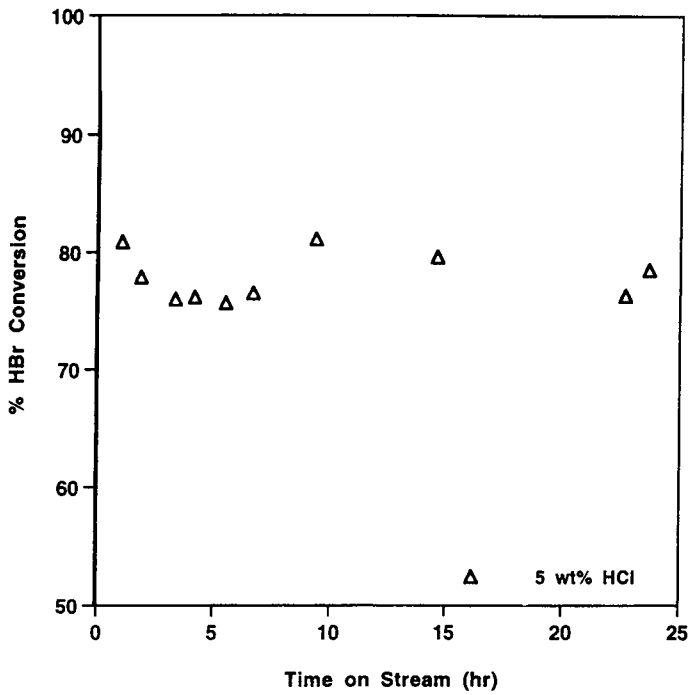

Fig. 5. Catalyst stability testing at partial conversion using an HBr feed stream containing 5 % HCl.

The high-conversion bromine product quality tests at 300°C and 335°C gave greater than 99 % HBr conversion. Analysis of the resulting bromine showed no detectable chlorine.

The positive results at 5 % HCl led us to attempt complete HBr conversion at even higher HCl concentration. We prepared and tested an equal molar aqueous HBr : HCl solution (30.3 wt % HBr : 13.6 wt % HCl) using 7 g of catalyst and a 6

ml/hr feed rate at an inlet temperature of 335°C. Complete conversion of the HBr was again observed. These results suggest that HCl has little effect on catalytic HBr oxidation.

Organic Contaminant Testing

Catalyst stability studies were conducted using a variety of model feeds. The results using 0.7 wt % propionic acid in aqueous HBr demonstrate the effectiveness of operating at partial conversion to monitor deactivation. Figure 6 shows that at 292°C, the propionic acid-contaminated feed caused rapid deactivation. Subsequent analysis of the catalyst showed carbon deposits on the catalyst.

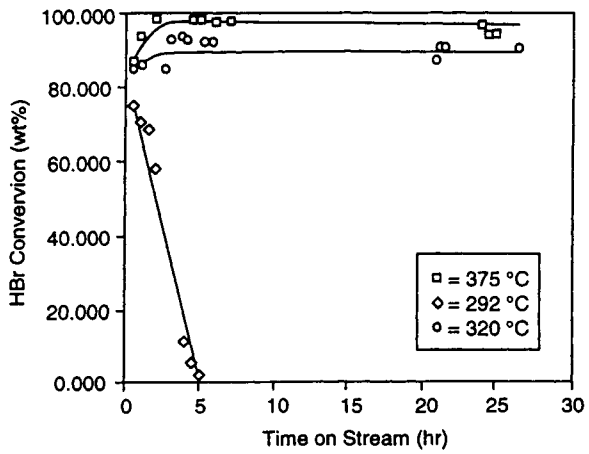

Fig. 6. Catalyst stability testing at partial conversion using an HBr stream containing 0.7 % propionic acid.

No attempt was made to measure CO_2 in these experiments. By increasing the temperature to 320°C, catalyst deactivation was prevented, and no carbon residue could be detected on the spent catalyst. Thus, temperature can be expected to significantly shift the reaction pathways of organic contaminants. In this study, and in all other studies, excellent corrosion resistance was observed for the corrosion coupons.

Only the propionic acid-contaminated HBr gave catalyst deactivation under the conditions tested. Figures 7 and 8 show the results of the dibromoethane, dichloroethane, phenol, and fluorobenzene tests.

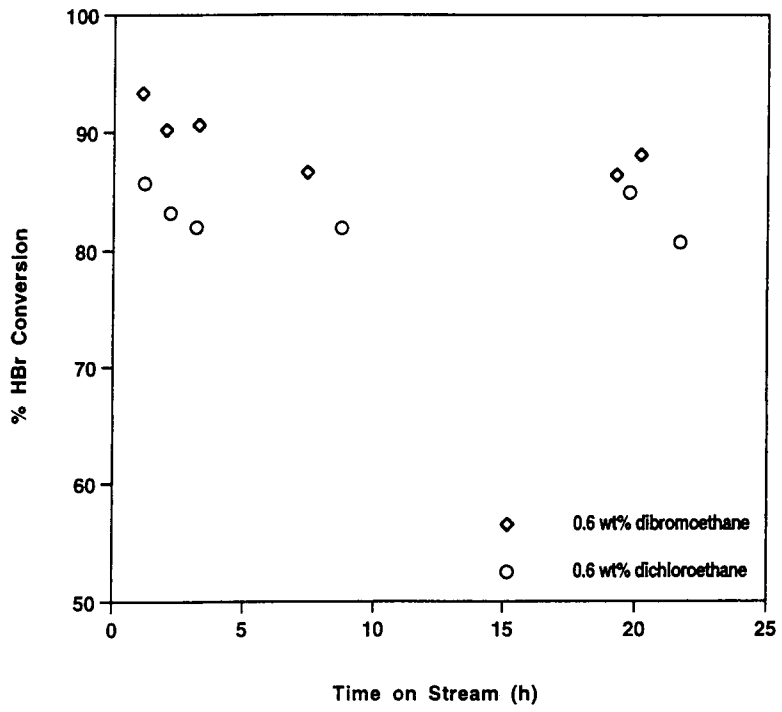

Fig. 7. Catalyst stability testing at partial conversion using an HBr stream containing 0.7 % propionic acid

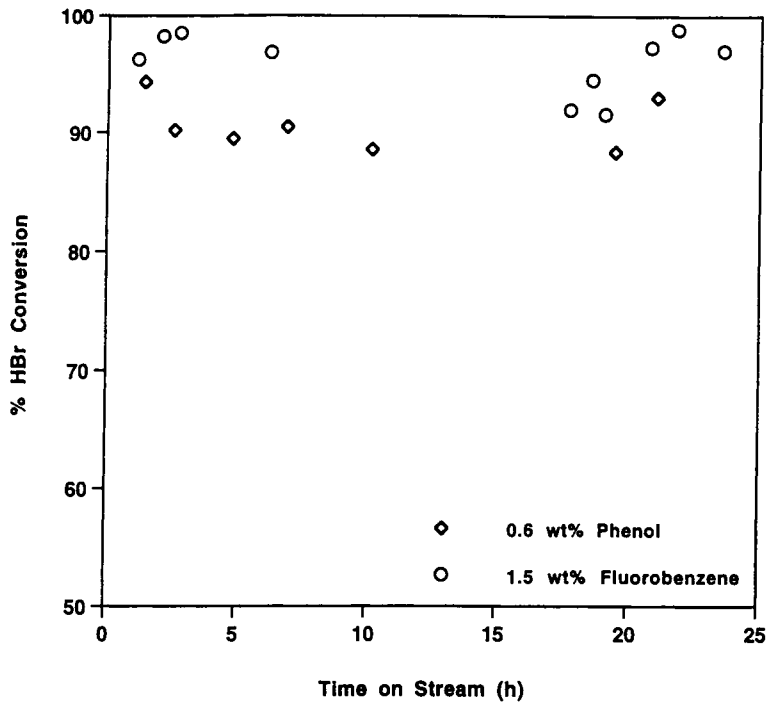

Fig. 8. Catalyst stability testing at partial conversion using phenol- and fluorobenzene-contaminated HBr feeds.

Similar results were obtained with dibromoethene and dichloroethene. The considerable variation in conversion observed among the samples is believed to be due primarily to differences in the oxygen partial pressure in the tests. The oxygen partial pressure differences were a function of the amount of oxygen added to allow complete combustion of the organics and the actual amount of organic combusted.

It is clear from the analysis of gaseous reactor effluent that there were variations in the extent of organic contaminant combustion. Some carbon dioxide was observed in the effluent gas from the reactor in most of the tests. However, with fluorobenzene at 300°C we estimate that only about 2.5 % of the fluorobenzene was combusted based on the amount of CO_2 observed. This is in contrast to the 30 to 50 % combustion of dibromoethane, dibromoethene, dichloroethane, dichloroethene, and phenol that we observed.

The high-conversion test provided some insight into the fate of the contaminants beyond simple combustion. Again, the fluorobenzene was relatively inactive. FT-IR

and ^{1}H NMR of the phase separated and dried bromine product from the 335°C test showed that about 95 % of the organics present in the bromine were unreacted fluorobenzene. The remaining 5 % was composed of mixed brominated fluorobenzenes. No appreciable levels of organic contaminants could be detected in the aqueous phase.

The results on dibromoethane illustrate the effect of temperature on the fate of the organics. At 300°C, approximately half of dibromoethane present in the feed was combusted. The remaining organics were present exclusively in the bromine phase. FT-IR and ^{1}H NMR identified these species as about equal amounts of the starting dibromoethane and 1,1,2-tribromoethane, with traces of dibromomethane and other brominated compounds. Again, no organic contaminants were found in the aqueous phase. After reaction at 335°C, unreacted dibromoethane could no longer be found in the bromine product collected after reaction. However, a variety of more highly brominated alkyl compounds was present.

The dichloroethane-contaminated feed similarly gave a mixture of unreacted dichloroethane and other halogenated products. These halogenated products included small amounts of 1-bromo-2-chloroethane. No organics were found in the aqueous phase from this reaction. Again, the high-temperature reaction caused the consumption of all of the starting contaminant and yielded a more complex mixture of organics in the bromine.

The phenol-contaminated sample was unique in yielding bromine containing none of the starting contaminant. Analysis of the bromine by FT-IR and ^{1}NMR showed a complex mixture of brominated phenols and small amounts of other brominated hydrocarbons. The absence of phenol in the bromine product is not surprising, since phenol reacts with bromine at room temperature to make predominantly tribromophenol.

CONCLUSIONS

Recycle of HBr to bromine is highly desirable both from an economic and an environmental standpoint. Catalytic oxidation offers the potential to recycle HBr from contaminated waste streams to bromine. We have demonstrated that the oxidation catalyst is stable against deactivation by a wide range of contaminants found in waste HBr streams. Strategies to deal with the contaminants will depend on the recycle applications in which the catalytic oxidation unit serves.

In the case of HCl-contaminated feeds, we expect that the most economical operating mode will achieve less than complete HBr conversion. This will yield bromine that is essentially free of chlorine contamination and eliminate the need to

purify the bromine by distillation. The process effluent stream will then be a mixed HCl-HBr stream, where the ratio of the two acids depends on the starting HCl concentration and the actual conversion level chosen. The feasability of using, selling, or disposing of this stream will be site specific.

For the organic contaminants, the required bromine product quality will also be site specific. If the catalytic oxidation unit is dedicated to a single bromination process, phase separation and drying may be the only purification required. Contaminants in the recovered bromine which are either the starting materials or products of the original bromination reaction should not present a problem if present in bromine recycled to the bromination reactor. In this case, the catalytic reactor would be operated to minimize the formation of undesirable brominated byproducts. For example, if phenol is present in the waste HBr from a tribromophenol manufacturing process, minor tribromophenol contamination of the bromine recycled to the reactor should not be a problem. Similarly, fluorobenzene in bromine recycled to a fluorobenzene bromination process should not present a problem.

If the catalytic HBr oxidation reactor is required to serve as a central facility for recycling a variety of waste HBr streams and conditions that combust all of the organic contaminants cannot be discovered, then further bromine purification operations are probably required. The simplest operation is distillation of the bromine. Due to the high bromine vapor pressure, bromine distillation can be accomplished using relatively small equipment. This is expected to be a highly effective method of purification, particularly where the boiling points of any contaminants are greater than 10°C different from that of bromine. In other applications, absorption or extraction may be needed.

We believe that the importance of recycling HBr to bromine will increase as environmental regulations on other methods of handling waste HBr continue to tighten. We have shown that catalytic HBr oxidation is a commercially viable technology for recycle of waste HBr and have completed design of commercial-scale plants employing this technology. Pilot studies with a commercial waste HBr stream with relatively low levels of a variety of organic and inorganic contaminants demonstrated the stability of the catalyst under realistic operating conditions, established acceptable materials of construction for the reactor, and verified that effective heat management could be achieved. The current laboratory studies further indicate that the catalyst system is highly resistant to deactivation by much higher levels of contaminants in the HBr feed than tested in the pilot unit. Therefore, we believe this technology can be widely applied to commercial waste streams.

ACKNOWLEDGMENTS

The authors wish to acknowledge the contributions of Jeff L. Haris, Robert K. Sato, and Dianna O. Durieux for their work in characterizing the reactor effluent streams in the contaminant studies.

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BROMINE CHLORIDE PRODUCTION : STUDY IN A REACTION CALORIMETER

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BACKGROUND

Several advantages have been attributed to bromine chloride, warranting its use rather than bromine in certain cases. Such advantages may include :

a. faster reaction rates;
b. a higher bacteriological activity compared to bromine or chlorine;
c. a higher oxydation potential;
d. lower corrosivity;
e. a higher weight-percentage of reactive bromine;
f. a higher volability.

Several routes for producing bromine chloride have been examined. The reaction attains equilibrium in both the liquid and vapour phases :

$$Br_2 + Cl_2 \rightleftharpoons 2\,BrCl \qquad (1)$$

The production process chosen in this work involved at least bromine in the liquid phase. In order to implement a production process, it is important to have knowledge of the reaction's kinetics, i.e. how soon is the equilibrium attained. In cases where the BrCl should be used immediately following its production, it is important to avoid high levels of unreacted chlorine, since it might result in undesired chlorinations etc.

Little has been reported on the kinetics of this reaction in the liquid phase; in one experiment at - 50°C, it has been reported that equilibrium was established within 30 seconds. It has been reported that the formation of BrCl in polat solvents is much faster than in non-polar solvents (ref. 1); hence, for the next reaction, one might expect some auto-catylitical behaviour. It was also reported in a review

(ref. 1) that equilibration in the gaseous phase, in the dark, could take 16-60 hours, whereas in carbon tetrachloride it could take seconds.

Values of the equilibrium constant $K = [BrCl]^2/([Br_2][Cl_2])$ in the gaseous phase have been determined experimentally; values were typically in the range 6.57-9, with 40-46 % dissociation at room temperature (ref. 2). The weak temperature dependence of the equilibrium constant indicates low heat of reaction; indeed, it has been calculated from equilibrium data to be - 0.406 kcal/mole BrCl (ref. 2).

For the liquid phase, the equilibrium ratios have only been estimated. For the range 233-263° K, its value was estimated in the range 4.5-5. corresponding to ca. 48 % dissociation. The heat of reaction in liquid phase was calculated to be in the range 0.624-0.756 kcal/mole (ref. 2).

The heat of formation of BrCl has been reported in one source to be 0.23 kcal/mole (ref. 1) and 3.06 kcal/mole in another (ref. 4). The difference was probably a different set of references states in (ref. 1).

In order to investigate the kinetics, heat of reaction and other aspects of the system, the RC1 reaction calorimeter was employed. This system allows to perform the reaction in a 2 liters glass reactor, while controlling the reactor and jacket temperatures. Following the reaction, the heat released at any time period can be determined. The operation and application of this system has been discussed in numerous publications (refs. 5,6).

DESCRIPTION OF THE PROCESS

Gaseous chlorine, under room temperature, was bubbled into liquid bromine maintained at -5°C. Excess chlorine left the reactor through a vent into an absorption column. The chlorine addition rate was adjusted to the reactor's cooling capacity, to prevent the temperature from rising above 0°C.

The end of the reaction was determined by two means :

a. The heat flux from the reactor - as the reaction approached completion, the heat flux decayed;

b. The volume of the liquid in the reactor - the volume should increase by a factor of 1.92 during the reaction.

RESULTS AND ANALYSIS

Heat Transfer Coefficients

Values of the heat transfer coefficient in the reactor side were determined. Stirring with an anchor stirrer at 100 RPM, the value obtained for bromine at - 5°C is 115 W/m^2-K and for BrCl at - 10°C : 190 W/m^2-K.

Heat Capacity

The heat capacity of bromine chloride was determined to be 23 cal/(grmol-K), compared to a value of only 8.4 cal/(grmol-K) stated elsewhere (ref. 1). The experimental result should not be trusted in this case, since its measurement was made under conditions where vaporization is considerable. The measurement will be repeated under pressure.

Analysis of the Heat of Reaction

The heat flux measured during the reaction was integrated. The heat of reaction at - 10°C has thus been calculated as 2.84 kcal/gr-mol "product BrCl". Since for each mole of BrCl 0.5 moles chlorine needed to be condensed and cooled from room temperature, releasing a heat of 2.54 kcal/gr-mol, the heat of reaction from liquid chlorine at the same temperature would be 0.3 kcal/gr-mol "product BrCl". For the degree of dissociation quoted above, i.e. 48 %, the heat of reaction in the liquid phase is obtained as 0.6 kcal/gr-mol, in conformance with the data in (ref. 2).

Kinetics of the Reaction

The heat flux during the reaction can be seen in Figure 1 below. It is clear that heat evolved immediately upon feeding the chlorine. There is no sign of the rate rising at any point during the reaction, so that no autocatalytical behaviour can be identified. The overall reaction times was ca. 3 hrs, based on both heat flux and volume change; towards the end of the reaction, the rate exhibits a continuing decay.

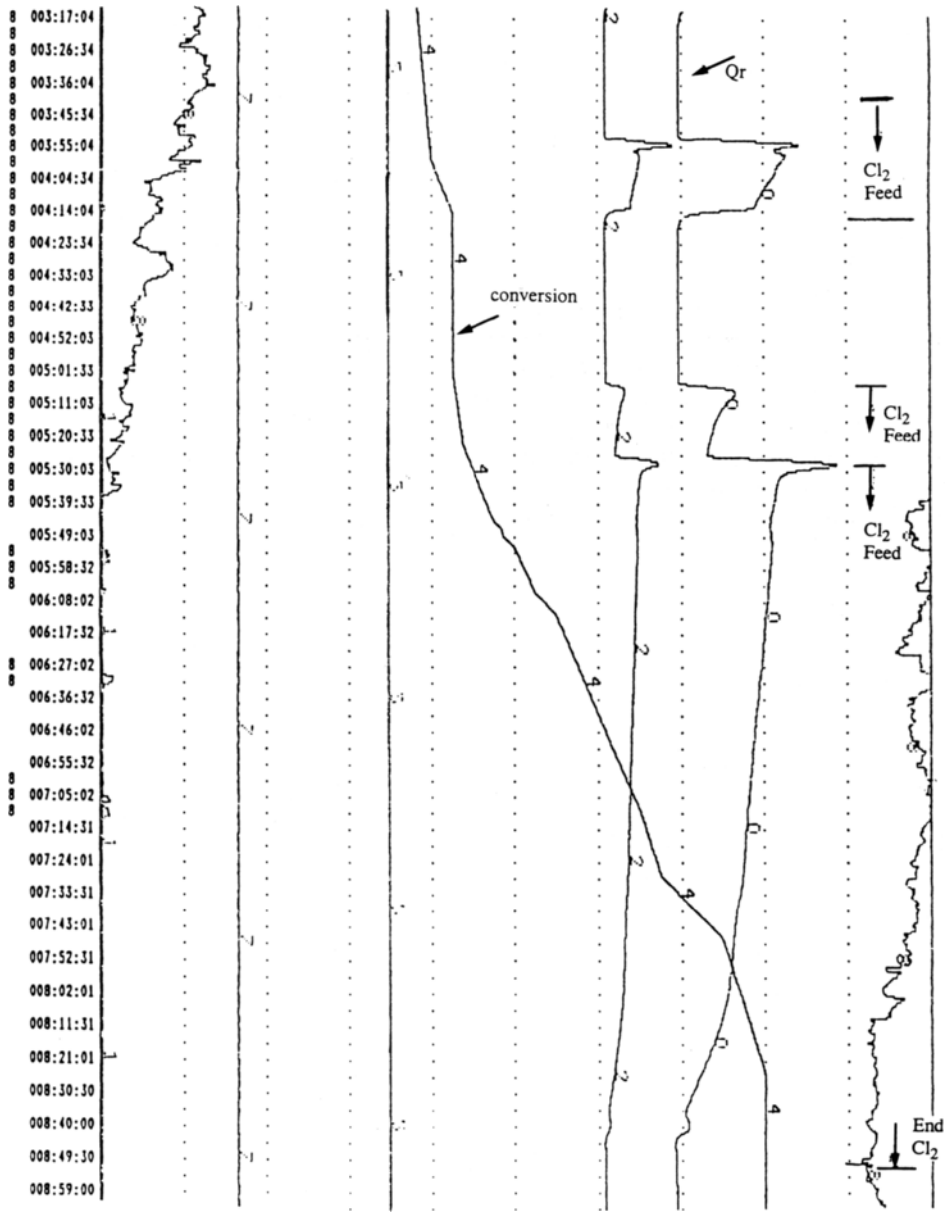

Fig. 1. Calorimetric Profile of the Reaction

CONCLUSION

The reaction was shown to undergo decay untill equilibrium is attained; autocatalytical behaviour could not be identified. The volume change is a good measure for the extent of reaction.

Due to the large contribution of the condensation of chlorine to the heat of the reaction, the heat of reaction and the kinetics may require further study under pressure, with liquid chlorine as one of the reagents.

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INFLUENCE OF BROMINE-CONTAINING FIRE RETARDANTS ON THE PROCESSING AND PROPERTIES OF PLASTICS

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ABSTRACT

The processing heat stability of most fire retardant plastics is lower than that of non-retarded plastics. Some compromises between processing heat stability and flame-retardancy are demonstrated in the following examples :

- the use of higher melt flowability of fire retardant-plastics to reduce processing temperature, for example brominated epoxy in acrylonitrile-butadiene-styrene terpolymer;
- heat stabilization of fire retardants, for example stabilized hexabromo-cyclododecane in high impact polystyrene and in polypropylene;
- the use of fire retardant mixtures and polymer property enhancers, for example in fire retardant-acrylonitrile-butadiene-styrene terpolymer (ABS).

Proper selection of plastic matrix fire retardants and property enhancers offers acceptable combinations of impact properties and heat-distortion temperature (HDT) values for fire retardant plastics. This can be demonstrated by fire retardant styrenics. Fire retardant enhancers have special interest as property enhancers : for example the addition of a highly flammable material such as ethylene propylene diene terpolyer (EPDM), dramatically improves the bromine efficiency of octabromodiphenyl oxide in ABS by increasing char-forming without changing the Sb-Br reaction.

INTRODUCTION

An application of fire retardants in plastics solves the problem of plastics flammability efficiently but usually creates problems with plastics processing and with plastics properties. In this paper we intend to evaluate various solutions to these problems.

MATERIALS AND METHODS

Materials and methods used in this study are given in Table 1 and Table 2 respectively.

Table 1. Materials used in this study

Acronym	Trade Name	Source	Description
ABS	NOVODUR P2 HAT	BAYER	General purpose acrylonitrile-butadiene-styrene terpolymer
	NOVODUR P2 K	BAYER	High impact acrylonitrile butadiene-styrene terpolymer
	RONFALIN TZ 110	DSM	High impact acrylonitrile butadiene-styrene terpolymer
HIPS	VESTYRON 638	HUELS	General purpose high impact polystyrene
PP	ELTEX P HV206	SOLVAY	General purpose polypropylene
	HIPOL J 400	MITSUI	General purpose polypropylene
SMA	STAPRON S SM-200	DSM	Styrene-maleic anhydride copolymer
EPDM	VYSTALON 3708	ESSO	Ethylene-propylene-diene terpolymer
TPE	VARIOUS	VARIOUS	Thermoplastic elastomer
FR-2016	FR-2016	DSB	Brominated epoxy
FR-2916M	FR-2016M	DSB	Modified brominated epoxy
HBCD	FR-1206HS	DSB	Heat stabilized hexabromo cyclododecene
	FR-1206/46	DSB	
DECA	FR-1210	DSB	Decabromodiphenyl oxide
OCTA	FR-1208	DSB	Octabromodiphenyl oxide
T6385	T6385	DSB	Proprietary fire retardant
TBS	FR-803	DSB	Tribromostyrene
MHO	MHRM-120	DSB	Surface treated magnesium hydroxide
	MHRM-640	DSB	
AO	VARIOUS	VARIOUS	Antimony trioxide

Table 2. Test methods and equipment

Property	Method	Apparatus
Flammability	UL-94 vertical burning test	Flammability hood as recommended by UL
Flowability	MFI : melt flow index, ASTM D 1238 Procedure A	Extrusion plastometer
	SF : Spiral Flow index, the length of specimen molded into spiral mold	Injection molding machine. Allrounder 221-75-350 Arburg
Izod nothed impact energy	Impact resistance of plastics and electrical insulating materials ASTM D-256-91	Pendulum impact tester type 5102, Zwick
HDT : heat deflection temperature under flexural load (1820 kPa)	Heat distortion test (HDT) ASTM D-648-72	CEAST 6005
Color deviation	Color measurement + comparison with white reference	Spectro color meter CS-3 ACS
Phase composition	X-ray diffraction	Philips diffractometer with Cu fine-focus tube
Morphology	SEM : scanning electron microscopy	JEOL scanning electron microscope

DISCUSSION

The major problem of most flame retarded plastics is a decrease in processing heat stability. A method recommended by several producers of plastics to solve this problem is to decrease process temperature (Table 3).

Table 3. Temperatures of Injection molding for various FR and NR plastics

Polymer	Producer	Trade name cycolac GSM	Flame retardancy	Temperature of injection molding recommended by producer (°C)
ABS	GENERAL ELECTRIC	CYCOLAC GSM	NR	232-260
		CYCOLAC KJT	FR	204-226
		CYCOLAC KJW	FR	193-232
		CYCOLAC KJV	FR	210-240
HIPS	BASF MONTEDISON SHULMAN		NR	200-274
			FR	200-232
PET	ALLIED ENGINEERED PLASTICS	PETRA-130	NR	260-310
		PETRA-130FR	FR	271-299
PA6		CAPRON 8200 HS	NR	227-271
		CAPRON XPN 1503	FR	216-260

FR = Fire Retardant NR = ?

However this solution is not always convenient and may prevent high productivity and/or the production of intricate forms which require high temperature processing. Fortunately, some fire retardants dramatically increase the flowability of fire retardant plastics melts. For example ABS, flame retarded with F-2016 or F-2016M (brominated epoxy) has much higher flowability, melt flow index (MFI), and spiral flow index, than virgin ABS (Fig. 1).

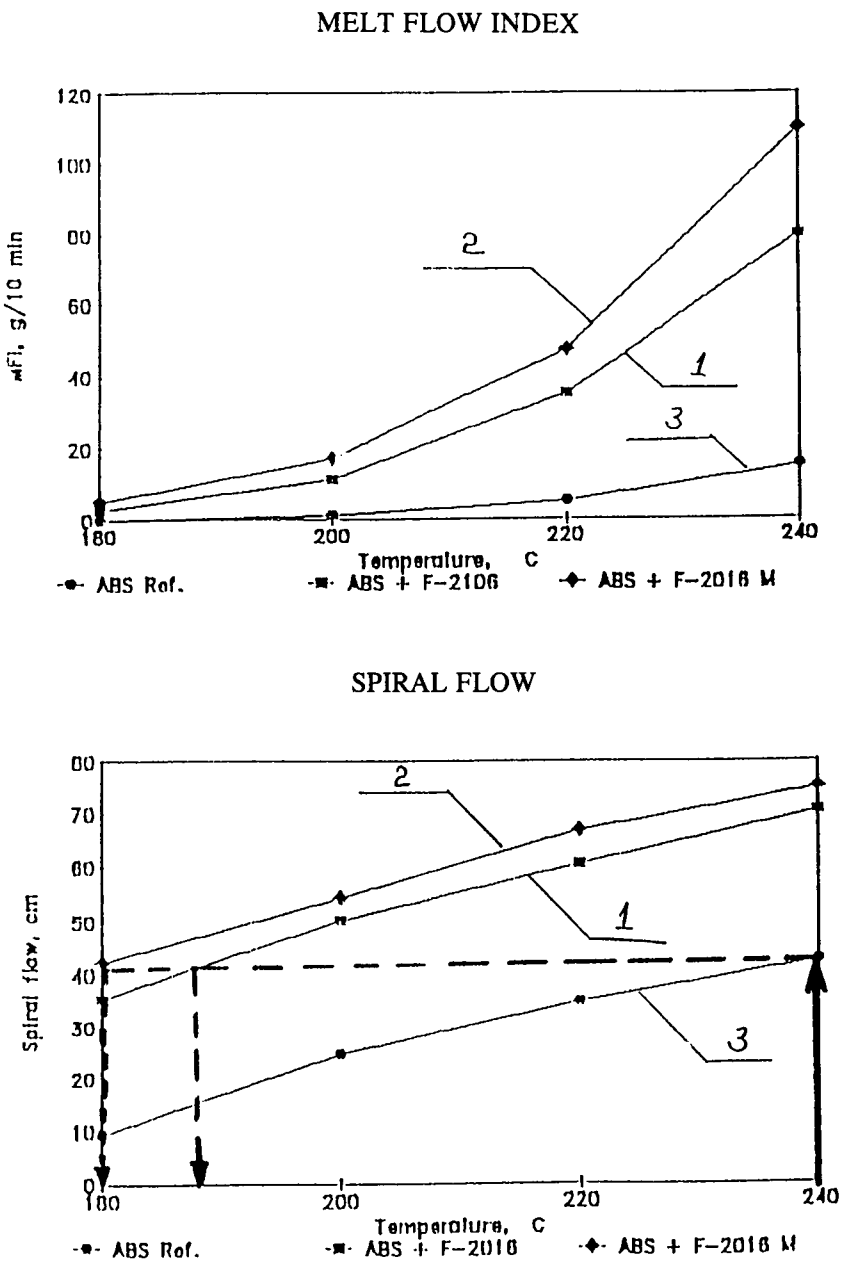


Fig. 1. Flowability of ABS/F2016 (1) and ABS/F-2016M (2) vs.virgin ABS (3)

This increase in the flowability of fire retardant plastics melts compensates for lack of heat stability by providing the same technological potentialities as high processing heat stability using low temperature processing (Fig. 2).

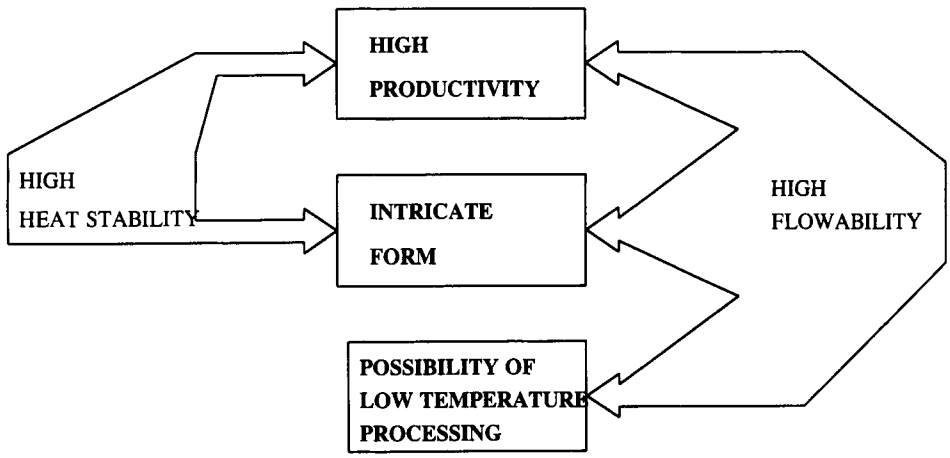
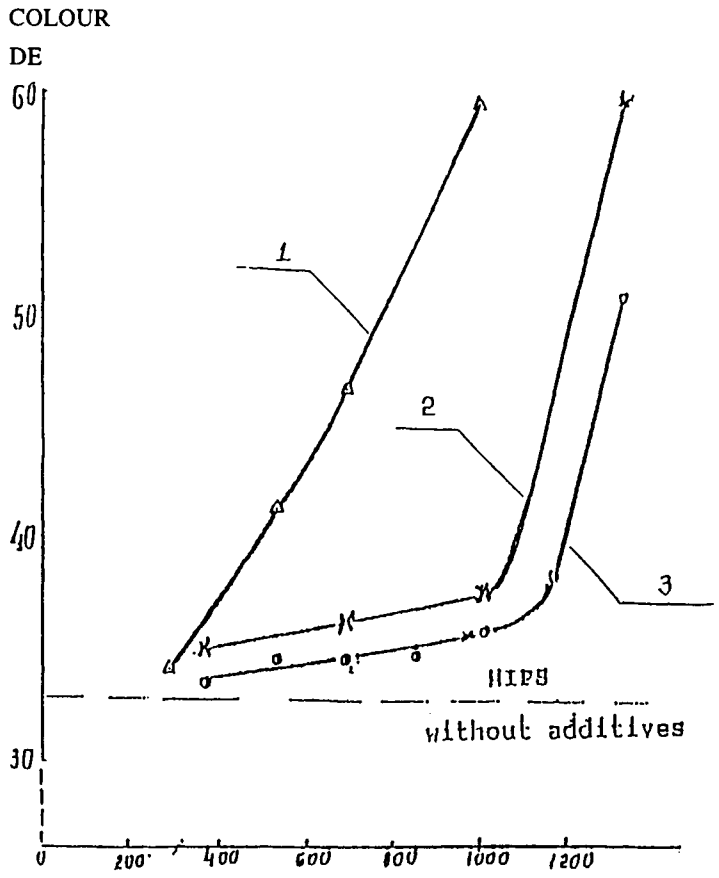


Fig. 2. Potentials provided by high heat stability and by flowability of plastics melt.

Another method of overcoming the poor processing heat stability of fire retardant plastics is to use heat stabilized fire retardants. The success achieved in the heat stabilization of hexabromocyclododecane (HBCD) is a good example of this approach. The processing heat stability of non-stabilized HBCD does not exceed 200°C (ref. 1) whereas heat-stabilized HBCD containing high impact polystyrene (HIPS) can be produced at temperatures up to 230°C (refs. 2,3). Figure 3 demonstrates the heat stability of HIPS/HBCD at injection molding.



1 = HBCD commercial
2 = Low-melting heat stabilized FR-1206-HS
3 = High-melting heat stabilized FR=12-6-HS

Fig. 3. Comparison of processing heat stability at 230°C of HIPS/HBCD

The application of FR-1206-HS ex Dead Sea Bromine Group provides longer residence time at 230°C without discoloration than the commercial heat-stabilized HBCD. The application of heat-stabilized FR-1206 was further developed by its use in fire retardant polypropylene (ref. 4). The new heat-stabilized HBCD, FR-1206/46, provides polypropylene with even better heat stability than FR-1206-HS (Table 4).

Table 4. Processing heat-stability of PP/FR-1206HS vs PP/FR-1206/46

COMPONENTS			FORMULATIONS - 27167		
			1	2	4
POLYPROPYLENE		%	96.4	96.4	99.3
FR-1206/HS		%	2.2	--	--
FR-1206/46		%	--	2.2	--
ANTIMONY TRIOXIDE		%	0.7	0.7	--
ADDITIVES		%	0.7	0.7	--
NOTCHED IZOD IMPACT		J/m	45.2	45.5	36.8
COLOUR	AS MOLDED at 240°C		29.8	29.7	--
	AFTER SUDDEN STOP 5 min. at 240°C		40.4	32.3	--

It should be mentioned that fire retardant-polypropylene has higher impact energy than polypropylene without HBCD and this improved impact energy resulting from the addition of fire retardant is a rare phenomenon. Usually the addition (15-25%) of low molecular components decreases the high impact properties of plastics although we know that HIPS flame-retarded with decabromodiphenyl oxide (DECA), for example, has almost the same impact energy as non-retarded HIPS (Table 5).

Table 5. VO HIPS/DECA vs NR HIPS.

COMPONENTS			FORMULATIONS - 6777	
			9	7
HIPS		%	100	84.4
KIND OF FR			NO	DECA
LOAD OF FR		%	0	12.0
ANTIMONY TRIOXIDE ANTIOXBLUE STAR "G" EX CAMPINE		%	0	3.6
BROMINE			0	10
UL-94 (3.2 MM)			NR	VO
ISOD	UNANNEALED		100	102
NOTCHED	ANNEALED (24 h @ 65°		107	101
IMPACT,J/m				
HDT, °C	UNANNEALED		68.0	66.8
	ANNEALED (24 h. @65°		80.7	77.9

The equally good performance of DECA may be related to its amorphization during processing in HIPS. From Figure 4 it may be seen that clear peaks of crystalline DECA (1) are absent from X-ray diffractogram of HIPS/DECA (2) whereas the peaks of Sb_2O_3 are clearly observed in both cases at 27°-29°C. This amorphization is presumed to result both from the thermal effect and from shear stress during plastic processing. The influence of shear stress was demonstrated by partial amorphization of DECA subjected to manual grinding (3) (Fig. 4).

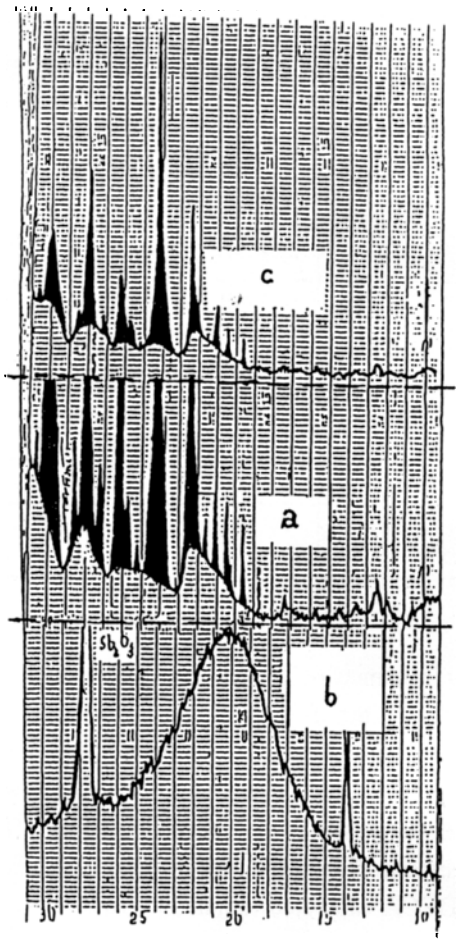


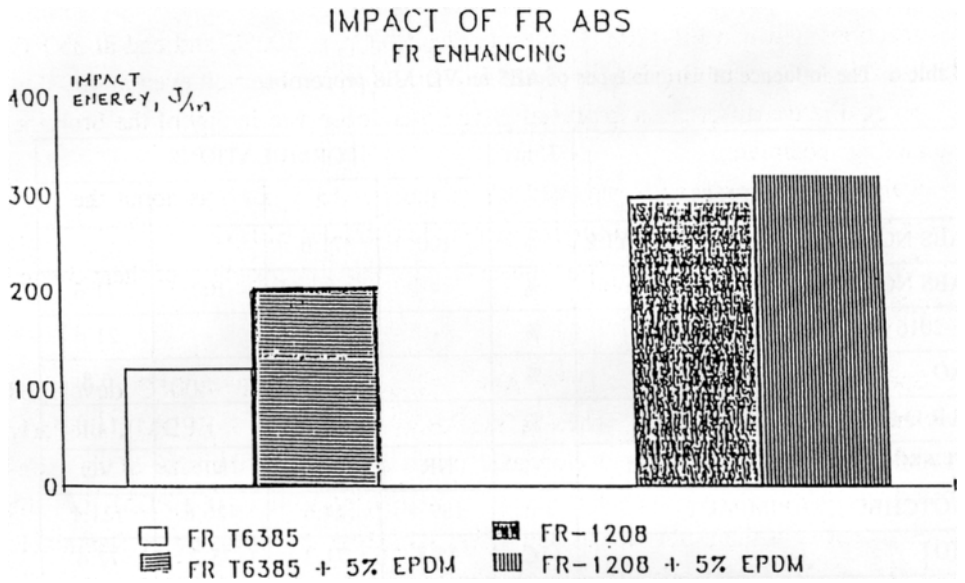
Fig. 4. X-ray diffractograms of DECA (1), HIPS/DECA+Sb_2O_3 (2), and manually ground DECA (3)

When the addition of fire retardant decreases the impact properties of plastics the correct choice of plastic may be crucial (Table 6).

Table 6. The influence of various types of ABS on VO ABS properties

COMPONENTS		Units	FORMULATIONS			
			1	2	3	4
ABS NOVODUR P2H-AT ex BAYER		%	100	71.6	-	-
ABS NOVODUR P2K ex BAYER		%	-	-	100	71.6
F-2016		%	-	21.6	-	21.6
AO		%	-	6.8	-	6.8
B R O M I N E		%	-	11.0		11.0
FLAMMABILITY UL-94 1.6 mm		-	NR	VO	NR	VO
NOTCHED IZOD IMPACT		J/m	189.4	24.6	426.6	121.1
HDT		°C	75.3	71.3	75.2	72.6
COLOR, DE	0 HOURS	-	16.4	16.5	26.9	12.3
	250 HOURS UV-Exposure	-	31.6	53.8	45.7	53.4

Impact energy can be further improved by the use of impact modifiers. In this approach the combination of impact improvement and fire retardant enhancing is of special interest (ref. 5). Figure 5 demonstrates this effect in ABS flame-retarded with commercial FR-1208 (octabromodiphenyl oxide) and with the proprietary FR-T6385.



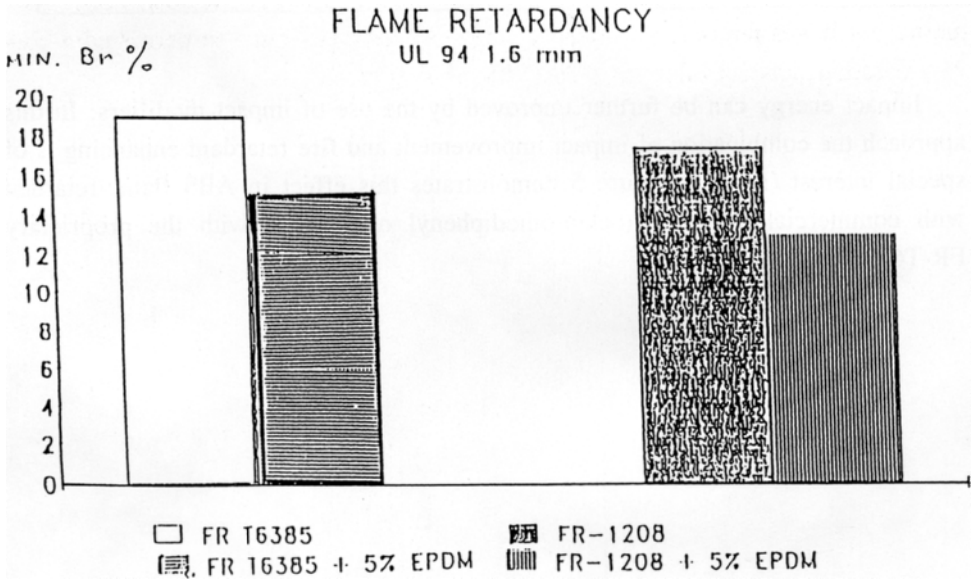


Fig. 5. Toughening and FR-enhancing of FR ABS

The study of the heat treatment of fire retardant ABS at temperatures close to ignition (Table 5) demonstrate the following :

- reactions between FR-1208 (Octa) and Sb_2O_3 start at 300°C and end at 350°C, whereas in ABS containing Sb_2O_3 alone no changes were observed even at 400°C.
- no qualitative differences in crystal phases were observed in any of the bromine-containing specimens.
- weight loss for VO ABS with EPDM, containing 13 % Br was about the same as for NR ABS with the same bromine content but without EPDM.
- The qualitative difference was observed in the morphology of heat-treated sample when SEM was used.

Specimens of NR ABS/(Octa + AO) heat-treated at 350°-400°C developed brittleness of connected pores, whereas VO ABS (Octa + AO + EPDM), similarly treated, was tougher with large elongated pores about twice the size of the non-treated specimen. Such behavior suggests an intumescent effect of EPDM, i.e. the development of a thick porous surface layer, inhibiting the diffusion of flammable products of plastic degradation towards the gas phase and heat transfer into the plactic mass.

Another example of the combination of toughening and fire retardant-enhancement is the use of TPE as a carrier for master batch of FR-803 (TBS). This master batch was not only an efficient toughener for SMA but also permitted a UL-94 VO rating, unachievable for SMA/TBS alone (Fig. 6).

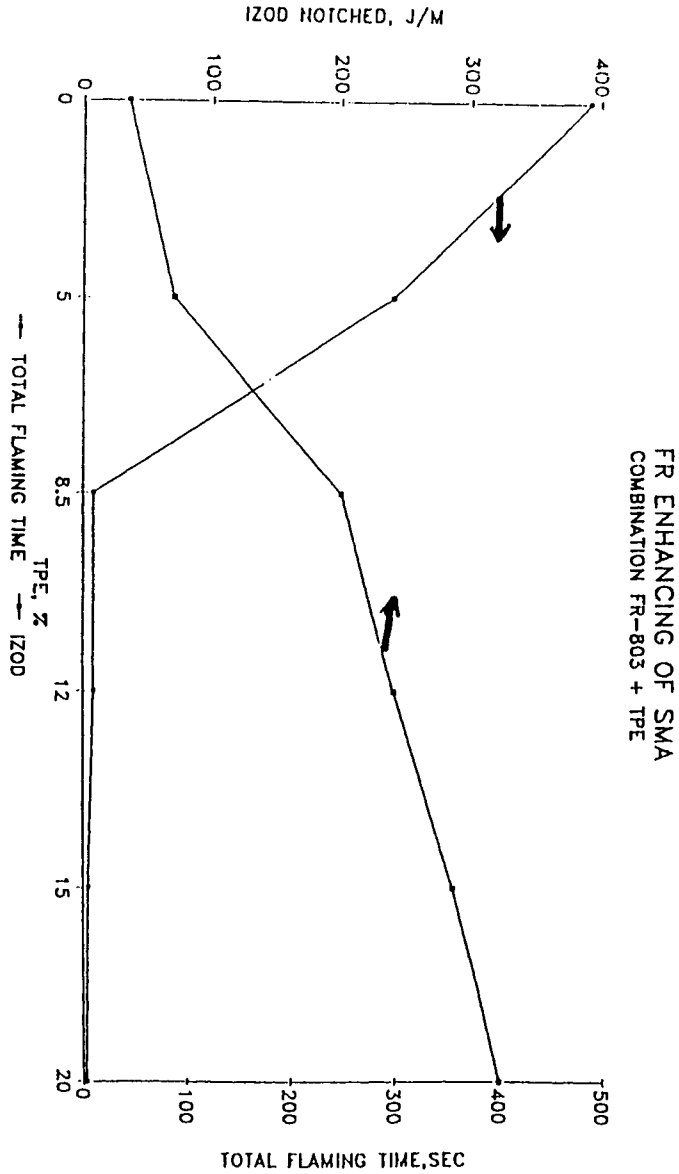


Fig. 6. The influence of TPE content on impact properties and on flammability of SMA/FR-803

It should be emphasized that only the addition of TPE/FR-803 master batch provided an efficient combination of toughening and fire retardant enhancement. The addition of TPE alone to SMA/FR-893, although providing a certain increase of impact properties, did not enhance the fire retardant (Fig. 7, Table 8).

Table 8. Toughening and fire retardant-enhancing of SMA/FR-803

COMPONENTS (%)		25697		
		10	9	7
SMA STAPRON S SM-200 ex DSM		73.5	58.5	58.5
FR-803 ex DSM		20	20	20
ANTIMONY TRIOXIDE		6.5	6.5	6.5
THERMOPLASTIC ELASTOMER (TPE)		--	15	15
COMPOUNDING		DIRECT COMPOUNDING OF ALL COMPONENTS		VIA MASTER BATCH
UL-94 1.6 mm	TOTAL FLAMING TIME, sec.	488	269	6
	MAX. FLAMING TIME, sec.	139	136	3
	NUMBER OF COTTON IGNITIONS	5	0	0
IZOD NOTCHED IMPACT, J/m		36	181	280
HDT °C		92	78	77

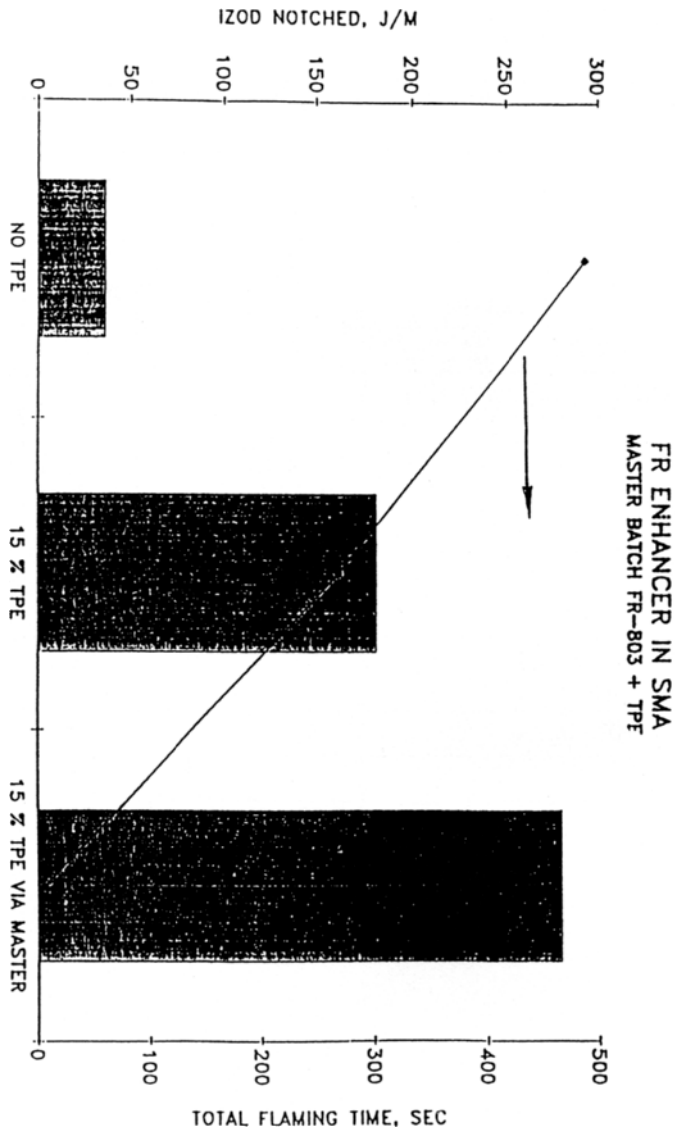


Fig. 7. Comparison between the influence of the addition of TPE to SMA/FR-803 and of TPE/FR-803 master batch to SMA.

The HDT value of VO SMA for TPE/FR-803 master batch is lower than for NR SMA/FR-803, resulting in a need for compromise between requests for thoughness and rigidity. This compromise may be achieved with filler-like FRs through the use of proper coupling agents. It can be seen in Figure 8 that VO PP containing magnesium hydroxide with different types of surface treatment has different impact and HDT values.

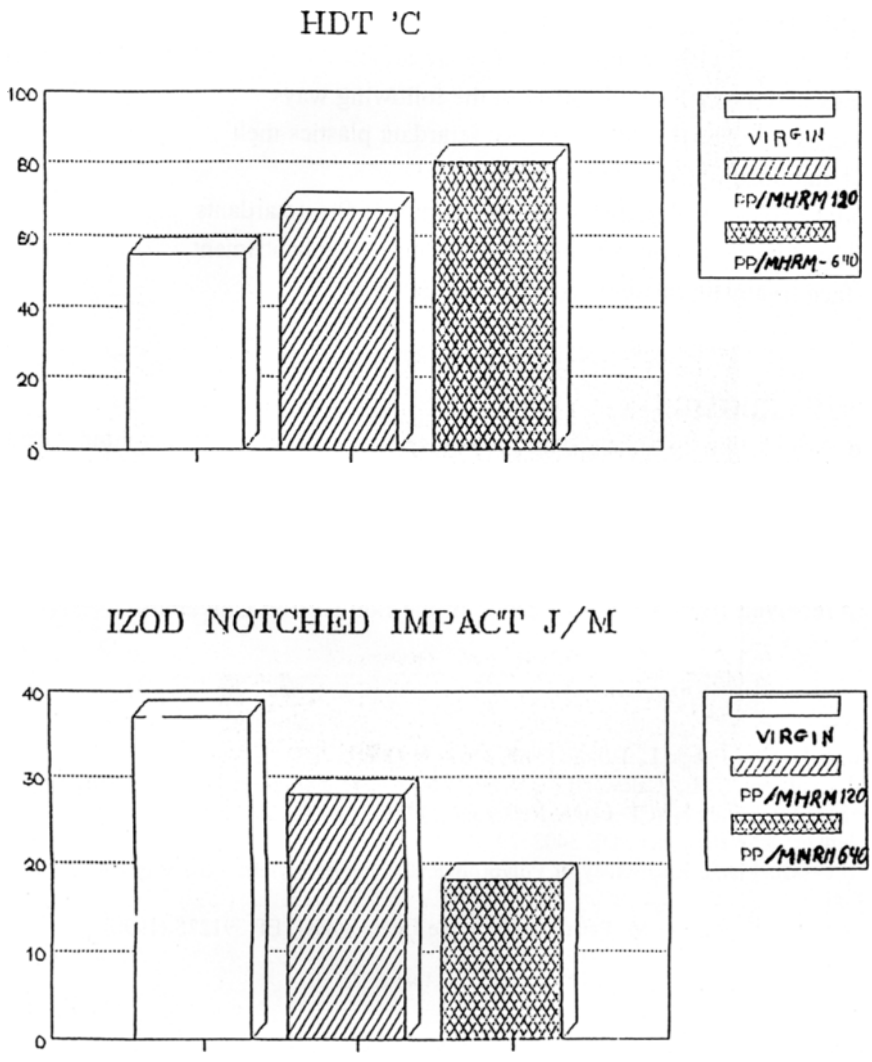


Figure 8. Use of magnesium hydroxide in PP

The correct selection of the kind of surface treatments renders possible very high HDT values (80°C) with impact of about 50 % of virgin polypropylene or, alternatively, lower HDT values (65°C) with the impact of about 70 % of virgin polypropylene. Even the latter kind of PP/$Mg(OH)_2$ has an HDT value higher than that of virgin polypropylene (55°C).

CONCLUSIONS

Problems of processability of fire retardant-plastics and resulting inferior properties may be efficiently solved in the following ways :

- the use of higher flowability of fire retardant plastics melt
- heat-stabilization of fire retardants
- proper choice of plastics for the application of fire retardants
- combination of toughening and of fire retardant-enhancement
- surface treatment of filler-like fire retardants.

ACKNOWLEDGMENTS

We would like to thank our colleagues at the Dead Sea Bromine Group : I. Finger, P. Georlette, E. Golan, S. Hini, D. Kallos, M. Manor, M. Scheinker, and D. Sondack, and S. Lach of the Ben Gurion University of the Negev for assistance in experiments and for their advice. We would like also to acknowledge the help received from the late L. Zevin of the Ben Gurion University.

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PHOSPHORUS-BROMINE FLAME RETARDANT SYNERGY IN ENGINEERING THERMOPLASTICS

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ABSTRACT

Phosphorus -bromine flame retardant synergy was demonstrated in a 2/1 polycarbonate/polyethylene blend. These data also show phosphorus to be about ten times more effective than bromine in this blend. Brominated phosphates, where both bromine and phosphorus are in the same molecule, were also studied. In at least one case, synergy is further enhanced when both phosphorus and bromine are in the same molecule as compared with a physical blend of a phosphorus and a bromine compound. On a weight basis, phosphorus and bromine in the same molecule are perhaps the most efficient flame retardant combination. The effect of adding an impact modifier was also shown.

INTRODUCTION

The mode of action of phosphorus-based flame retardants is believed to take place in either the condensed or the vapor phase (refs. 1,2) depending on the type of phosphorus compound and the chemical composition of the polymer. Phosphorus has been reported to be 3 to 8 times more effective than bromine depending on the polymer type (ref. 3).

Phosphorus/bromine combinations are perhaps the most effective flame retardant combination (ref. 3) and claims have been made for synergy. The formation of phosphorus trichloride or oxychloride has been postulated by analogy to that of the formation of antimony trichloride and oxychloride but there is no evidence for this mechanism. Some reports of synergy appear to be a result of a nonlinear response to the flame retardant concentration.

A mixture of bromine and phosphorus compounds was shown to be more effective in ABS resin than anticipated by the results obtained with the individual flame retardants. When bromine and phosphorus are in the same compound even higher oxygen indices were obtained. The data convincingly shows bromine/phosphorus synergy (ref. 4). Similar synergy was shown in high impact polystyrene (HIPS) and polymethyl methacrylate (refs. 5,6).

Surprisingly, phosphorus when combined with bromine is effective in non-oxygen containing polymers. In another reference, a mixture of a brominated compound and a triaryl phosphate was claimed to be effective in HIPS where antimony oxide is generally required as a synergist for bromine (ref. 7).

Work in these laboratories with a brominated phosphate flame retardant gave products with oxygen index values significantly higher than anticipated. The magnitude of the increase suggested possible phosphorus-bromine synergy. The polymers studied were modified polyphenylene oxide (a PPO/high impact polystyrene blend) and polycarbonate / ABS blends.

Convincing evidence for phosphorus/bromine synergy has now been found in a 2/1 polycarbonate/polyethylene terephthalate blend. Phosphorus and bromine blends were studied as well as compounds which have both elements in the same compound. The relative flame retardant efficiencies of phosphorus and bromine are also reported.

BACKGROUND

A comparison of bromine and phosphorus compounds on the flammability of PET fiber shows phosphorus (as phosphine oxide) to be 3.7 times more effective than bromine (Table 1). No synergy was observed. Nevertheless, phosphorus was shown to be more effective than antimony normally used as a synergist, resulting in a higher oxygen index at a lower concentration (Table 2).

Table 1. Oxygen Index of PET Fibers Containing Phosphorus or Bromine Flame Retardants[1]

% Br	% P	Oxygen Index
0	0	20.0
0	1	22.2
0	2	25.0
3.7	0	22.2
7.4	0	25.0
3.7	1	25.0

[1] Adapted from ref. 8

Table 2. Enhancement of Bromine Flame Retardancy by Antimony and Phosphorus in a PET Fiber[1]

% Br	% Sb	% P	Oxygen Index
0	0	0	20.0
6.1	0	0	22.5
6.1	1.3	0	24.8
6.1	0	0.9	25.5

[1] Adapted from ref. 8

A study of various types of flame retardants in a 40/60 blend of polyphenylene oxide and high impact polystyrene is shown in Table 3. Phosphorus flame retardants are highly effective in this resin blend, 1.1 % phosphorus giving a product with a 30.9 oxygen index and an UL-94 rating of V-0 at 1.6 mm. By contrast it takes 7.9 % bromine plus 2.5 % antimony oxide to give a product with an UL-94 V-0 rating; the oxygen index is only 27.0. The use of the brominated phosphate BrP 60/4 is particularly effective giving a product with an oxygen index value of 32.1 with only 10.7 % flame retardant and no antimony oxide. This product is also rated V-0 (ref. 9).

Table 3. Flame Retarding 40/60 Polyphenylene Oxide / High Impact Polystyrene Blend

Flame Retardant	BrPC	Phosphate Ester	BrP 60/4
Concentration, %	12.0	13.0	10.7
Antimony Oxide, %	2.5	-	-
Bromine, %	7.9	-	6.4
Phosphorus, %	-	1.1	0.4
Oxygen Index	27.0	30.9	32.1
UL-94 (1.6 mm) rating	V-0	V-0	V-0
sec.	1.8	5.0	3.6

The high flame retardant efficiency for the brominated phosphates was also observed in polycarbonate / ABS blends (ref. 10). All-phosphorus, all-bromine and brominated phosphate compounds were compared at 10 % concentration. A brominated phosphate gave a product with a significantly higher oxygen index than the other two flame retardants (Table 4). The UL-94 rating for the resin containing the brominated phosphate was V-0 at 1.6 mm whereas the other two compounds were rated UL-94 V-2. All three compounds contained 0.5 % fibrillated Teflon to inhibit dripping. Once again the question is additivity or synergy.

Table 4. Flame Retarding 3/1 Polycarbonate / ABS with 10 % Flame Retardant / 0.5 % Teflon 6C*

	TPP	BrPC	BrP 60/4
Oxygen Index	25.8	27.2	32.3
UL-94 1.6 mm, rating	V-2	V-2	V-0
sec.	8.1	6.7	2.6

* Brabender study

MATERIALS

The polycarbonate used was Lexan 141 from General Electric. Kodapak 9663 from Eastman Chemical is a bottle grade of resin. Two bromine flame retardants were evaluated, BC-52, a brominated polycarbonate oligomer chain-capped with phenol containing 51.3 % aromatic bromine and FF-680, bis-(tribromophenoxy) ethane containing 70 % bromine. Both products are available from Great Lakes Chemical in W. Lafayette, IN. Two phosphorus compounds were evaluated, triphenyl phosphate containing 9.5 % phosphorus and RDP, tetraphenyl resorcinol diphosphate containing 10.8 % phosphorus. Both compounds are available from FMC Corporation. Philadelphia, PA. Two brominated phosphates were evaluated, Reoflam PB-460 containing 4 % phosphorus and 60 % aromatic bromine, and Reoflam PB-370 containing 3 % phosphorus and 70 % non-aromatic bromine. These products are described in Table 5. The impact modifier used was Paraloid EXL-3607 from Rohm & Haas. Teflon 6C from duPont was used as a drip inhibitor.

Table 5. Description of Flame Retardants

Flame Retardant	Designation	% Br	% P	mp°C
Brominated Polycarbonate Oligomer	BrPC	51.3	-	210-230
bis-(tribromophenoxy) ethane	BrPE	70	-	223-228
Triphenyl phosphate	TPP	-	9.5	49
Tetraphenyl resorcinol diphosphate	RDP	-	10.8	liquid
Brominated phosphate 60/4	BrP 60/4	60	4	105
Brominated phosphate 70/3	BrP 70/3	70	3	180

FLAMABILITY TESTING

The oxygen index method was used to demonstrate synergy. This method measures ease of ignition, that is the facility with which a material or it's pyrolysis products can be ignited under given conditions of temperature and oxygen concentration. This test is indicative of the intrinsic flamability of a material but

tells very little about it's role in propagating a fire from one place to another. The heat in this test comes, after ignition, solely from the combustion of the sample itself. The oxygen index test provides a measure of the fire hazard. Flamability was also measured by the Underwriters Laboratories UL-94 method. In the former test the sample burns from the top down like a candle and the polymer adjacent to the flame remains relatively cool. In the latter test, the sample burns from the bottom up preheating the polymer beyond the flame zone.

PROCESSING

Most of the compounds were extrusion compounded in a conical, partially intermeshing, counter rotating twin screw extruder (Haake Reomix TW-100). The extruder speed was set at 50 rpm and the barrel temperature profile was set to produce a melt temperature of 260°C at the die. Samples were injection molded in a 31.8 MT Battenfeld press with a 59 cc shot size. Where noted, samples were compounded in a 60 cc Brabender internal mixer and compression molded.

RESULTS

A 2/1 blend of polycarbonate and polyethylene terephthalate (PC/PET) was flame retarded with bromine, phosphorus, a blend of bromine and phosphorus, and compounds containing both phosphorus and bromine in the same molecule. All compositions contained 0.5 % Teflon 6C as a drip inhibitor and where specified 5 % of an impact modifier.

The flame retardancy of a 2/1 PC/PET blend containing bromine (BrPC) and brominated phosphate (BrP 60/4) flame retardants was compared (Fig. 1). A compound with an oxygen index of about 32 requires 11 % of the brominated polycarbonate oligomer or 5.5 % of the brominated phosphate. In other words, a composition containing 3.3 % bromine plus 0.22 % phosphorus has the same oxygen index as a compound containing 5.6 % bromine. Figure 2 shows triphenyl phosphate and the brominated polycarbonate oligomer to be equally effective on a weight basis (Brabender study). The conclusion is that phosphorus is either significantly more effective than bromine or bromine and phosphorus are synergistic in this polymer blend. The consensus has been that bromine and phosphorus are additive.

Figure 1

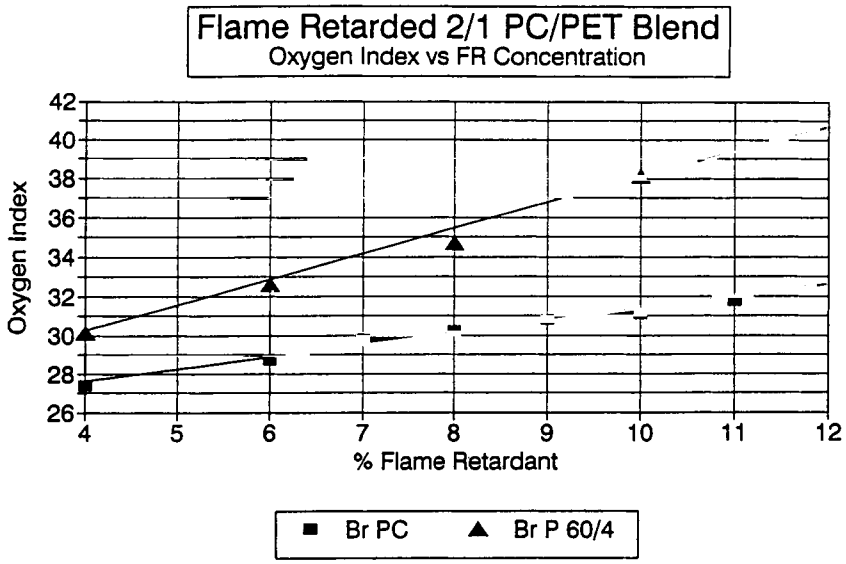
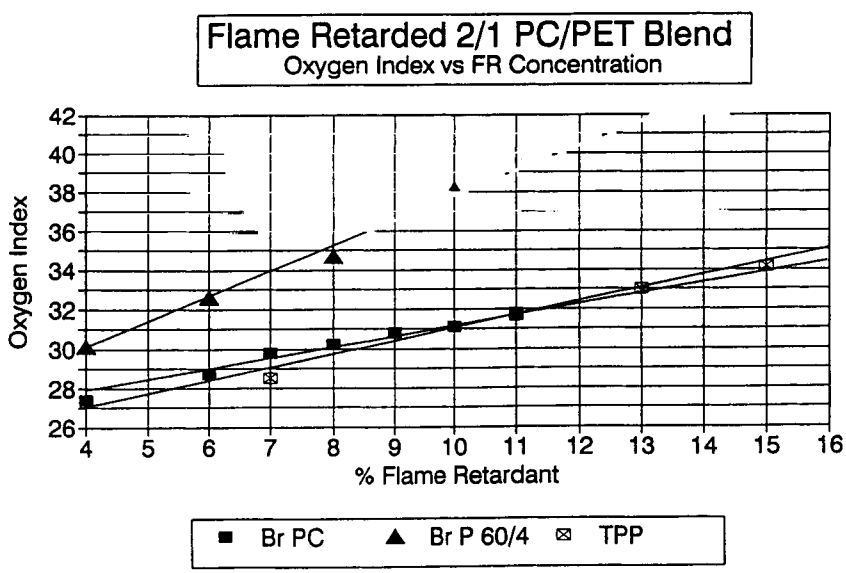
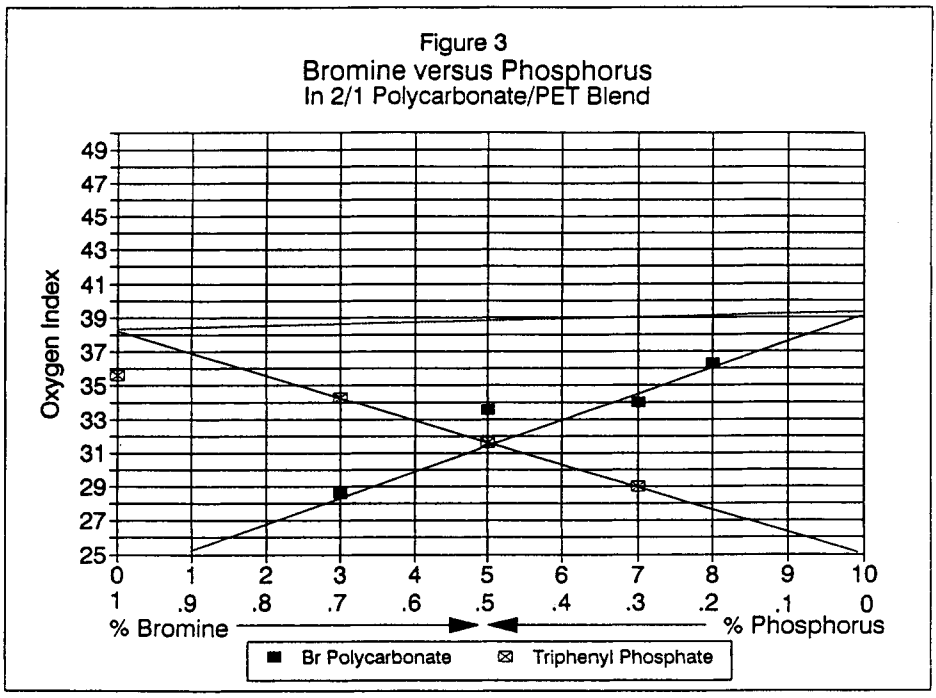


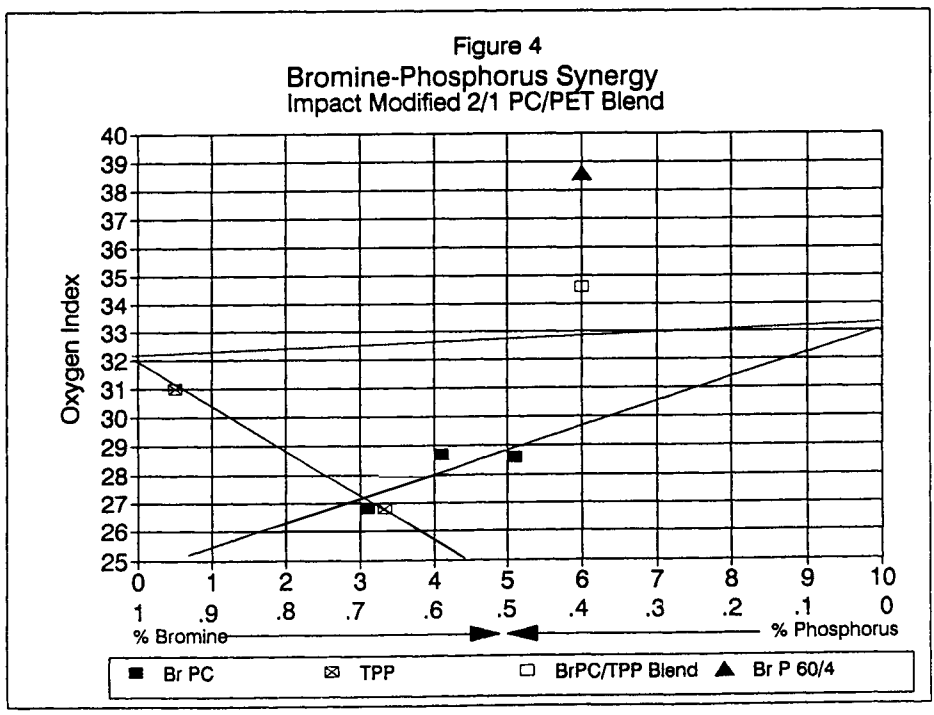
Figure 2



In Figure 3 where the BrPC and TPP are compared, the bromine concentration increases from left to right and the phosphorus concentration increases from right to left. The two curves intersect at 5 % bromine and 0.5 % phosphorus, indicating that phosphorus is ten times more effective as a flame retardant. At the extremes 1 % phosphorus is equivalent to about 9+% bromine.

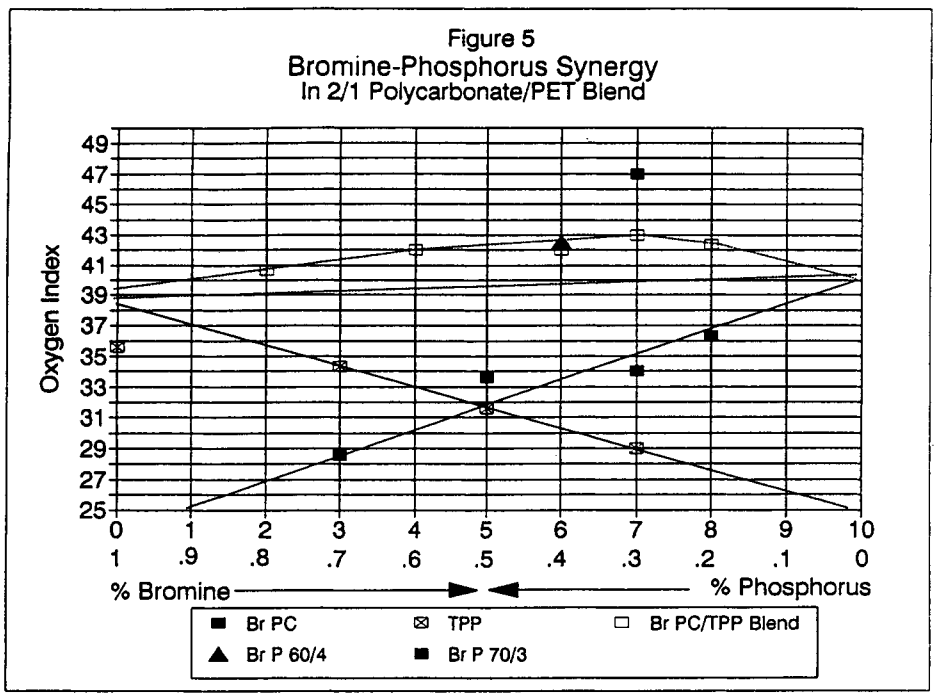


Since the BrPC and TPP curves are both linear, blends of bromine and phosphorus compounds would be expected to fall on the theoretical additives line shown as a dotted line. However, a mixture of BrPC and TPP with a composition of 6 % bromine and 0.4 % phosphorus gave an oxygen index value significantly higher than anticipated (Fig. 4). And when bromine and phosphorus are in the same compound, as in the brominated phosphate, an even higher value was obtained consistent with the reports of Yang and Lee (refs. 5-7). These data suggest that bromine and phosphorus are synergistic in this polymer blend. These compositions contain 5 % impact modifier and the oxygen index values are lower than shown in Figure 3.

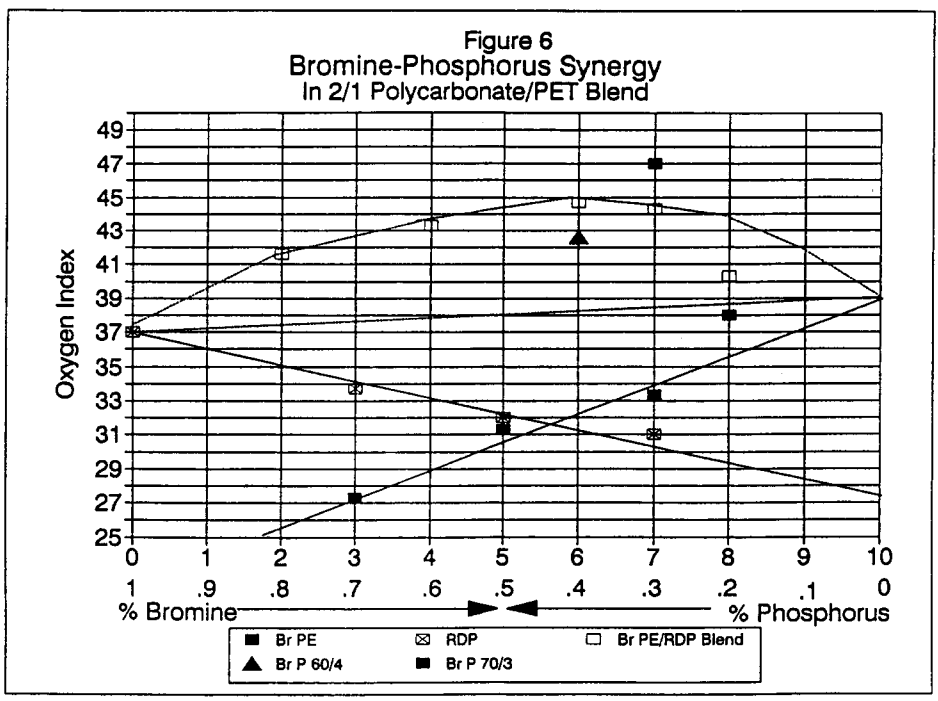


Various blends of BrPC and TPP were investigated. The resultant products all had significantly higher oxygen indices thant the theoretical addition curve (Fig. 5) demonstrating a strong positive synergy.

A brominated phosphate containing 70 % bromine and 3 % phosphorus gave an even higher oxygen index. As can be seen in Figure 5, the bromine/phosphorus ratio influences the degree of synergy since BrP 60/4 showed about the same degree of synergy as the blend.



Consideration was given to the specific additives chosen for this study. The brominated polycarbonate oligomer may be too stable and of low volability inhibiting the bromine from getting to the flame zone without the aid of antimony. As a result, a more volatile bromine flame retardant was also evaluated, specifically, bis-(tribromophenoxy) ethane (BrPE). Triphenyl phosphate is somewhat volatile at the processing temperature used and some of it might be lost in the compounding and molding steps. As a result a dimeric product was evaluated, specifically, tetraphenyl resorcinol diphosphate (RDP). The resultant data is shown in Figure 6. Data similar to those in Figure 5 were obtained with the exception that the synergy might be slighlty enhanced in Figure 6.



The data in Figure 7 compares the two bromine and the two phosphorus compounds. The differences obtained are small and may be experimental.

Figure 7

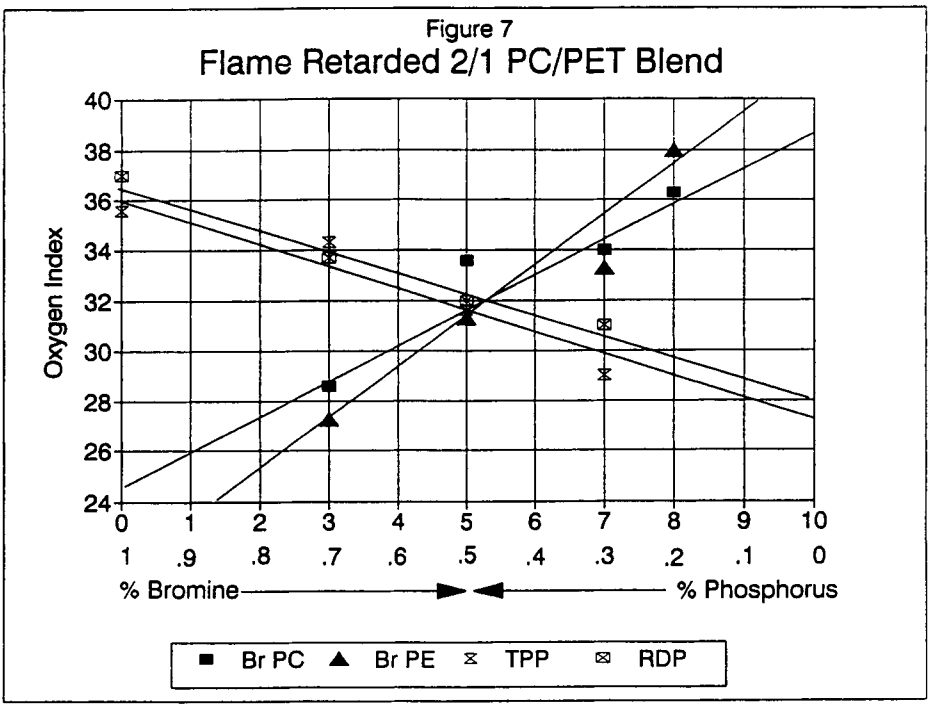


Figure 8 plots flame retardant concentration versus oxygen index for a resin containing 5 % impact modifier. At equivalent weight, triphenyl phosphate is significantly more effective thant the brominated polycarbonate oligomer. Blends of the two result in products with oxygen indices identical to those obtained with TPP alone. The concentration/oxygen index slope for the brominated phosphate is much steeper than for the other compositions. In summary, to obtain a resin with an oxygen index of 32 requires 16.7 % of the brominated polycarbonate oligomer, 12 % of the triphenyl phosphate, or 6 % of the brominated phosphate 60/4.

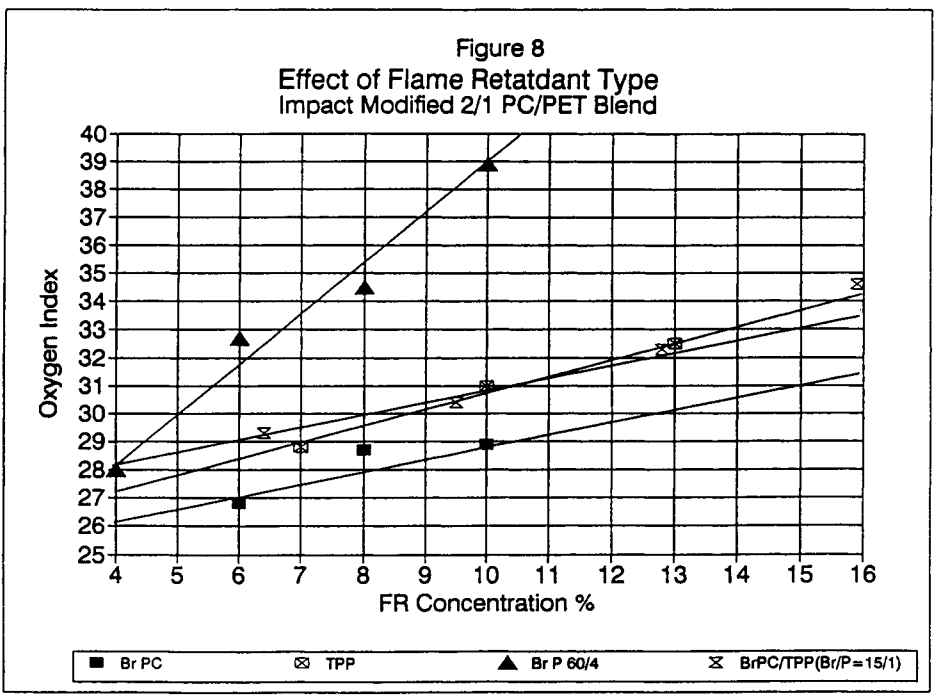


Table 6 shows the flamability characteristics of an impact modified 2/1 polycarbonate/PET blend containing 6 % of the various flame retardants. The composition containing the brominated phosphate 60/4 is the only one which is V-0 by the UL-94 vertical burn test. At 10 % add-on, the all-bromine containing resin is V-1 and at 13 % add-on the all-phophorus containing resin is V-0.

Table 6. Flame Retarding Impact Modified 2/1 Polycarbonate/PET Blend

Polycarbonate	59.3
PET	29.7
Impact Modifier	5.0
Teflon 6C	0.5
Flame Retardant	6

Flame Retardant	BrPC	TPP	BrP 60/40	BrP 70/3
Oxygen Index	24.9	28.5	29.5	28.9
UL-94, Rating	B*	B	V-0	V-2
sec.			2.0	6.2

* burns

CONCLUSIONS

Bromine/phosphorus synergy was investigated in a 2/1 polycarbonate/ polyethylene terephthalate blend. Synergy was demonstrated when blends of brominated and phosphorus compounds were used. The synergy is even more pronounced with a compound containing both elements in the same compound. This was dependant on the bromine/phosphorus ratio in the compound. Phosphorus was shown to be 9 to 10 times more effective than bromine in this resin blend.

ACKNOWLEDGEMENTS

I wish to acknowledge the excellent contributions of Charles A. Tennesen and Jose A. Vega for the compounding and the flammability studies.

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TREATMENT OF BROMIDE EFFLUENT PROBLEMS WITH H_2O_2 TECHNOLOGY

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INTRODUCTION

The majority of brominations carried out to produce organo bromine compounds create a bromide containing effluent. This is because only one half of the bromine molecule is incorporated into the product; the other bromine atom is discharged as hydrogen bromide or its inorganic salts creating a problem for industrial operators for any or all of three reasons. Firstly, there may be discharge limits which constrain how much bromide may be disposed of to drain. Secondly, it will have an adverse effect on process economics because only half the available bromine is being utilised and there are costs associated with treating the effluent. Finally, the presence of these effluents will have an adverse effect on the operator's environmental image.

ALTERNATIVE SOLUTIONS

There are several possible solutions to the problem of bromide effluent.

- Disposal
- Return to the supplier
- Process modification
- Recovery of bromine

Disposal

As already mentioned, the scope for direct disposal to drain can be limited by local regulations and will often involve costs. Whilst this may be an option at present, it will become less attractive in the future as discharge limits are tightened.

Return to the Supplier

There is the possibility of returning the waste streams to the original supplier for disposal or recovery. This is not always possible operationally and will be prohibited logistically where the user is geographically remote from the supplier.

Process Modifications

H_2O_2 can be added to these reactions to regenerate bromine in situ from the by-product HBr. This approach removes the problem at source. It will be discussed in more detail later but is an attractive option where the reaction is not adversely affected by the addition of water.

Recovery of Bromine

A final option for dealing with the bromide effluent problem is to recover the bromine for re-use giving a more environmentally acceptable effluent. The alternative approaches will be discussed in detail later, but H_2O_2 offers particular attractions in terms of giving a cleaner process.

HYDROGEN PEROXIDE BASED SOLUTIONS

Hydrogen peroxide is a versatile, safe and stable reagent. It is produced and used on large scales throughout the world and can be used over a wide range of conditions from acidic to alkaline and from organic to aqueous media.

Solutions of hydrogen peroxide are of high purity, readily transportable in bulk quantities and exhibit long-term storage stability over a wide range of conditions. When stored in compatible vessels under ambient conditions and free from contamination, solutions of 35 %, 50 %, or 70 % H_2O_2 concentration will lose less than 1 % of their available oxygen content within a year.

The bromination process where the problem to be addressed occurs is shown diagramatically below.

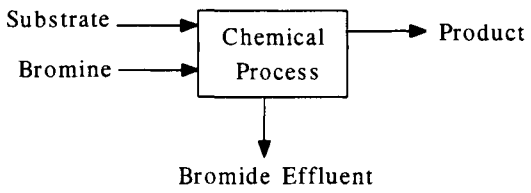


Fig. 1. Bromination Process

Hydrogen Peroxide can be used to either prevent the bromide effluent or cure it. Prevention is achieved by addition of the reagent to the process, cure by treatment of the effluent to recover bromine. In both cases the basic chemistry (ref. 1) is the same.

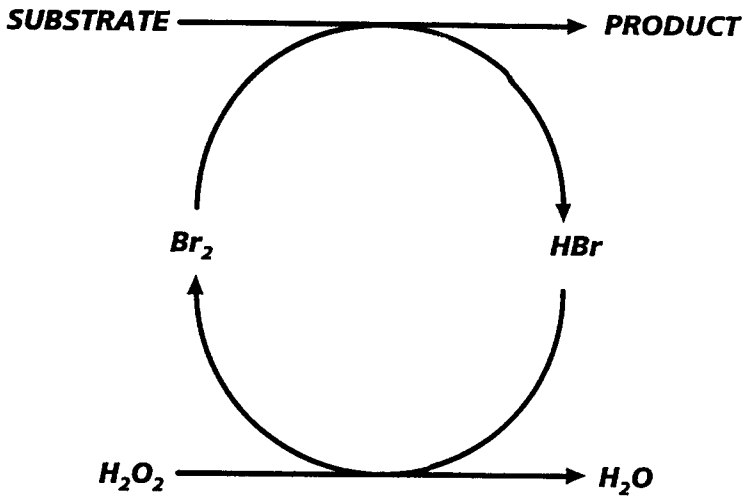
$$H_2O_2 + 2HBr \longrightarrow Br_2 + 2\,H_2O$$

The reaction is rapid and produces bromine efficiently.

Prevention of Bromide Effluent using H_2O_2

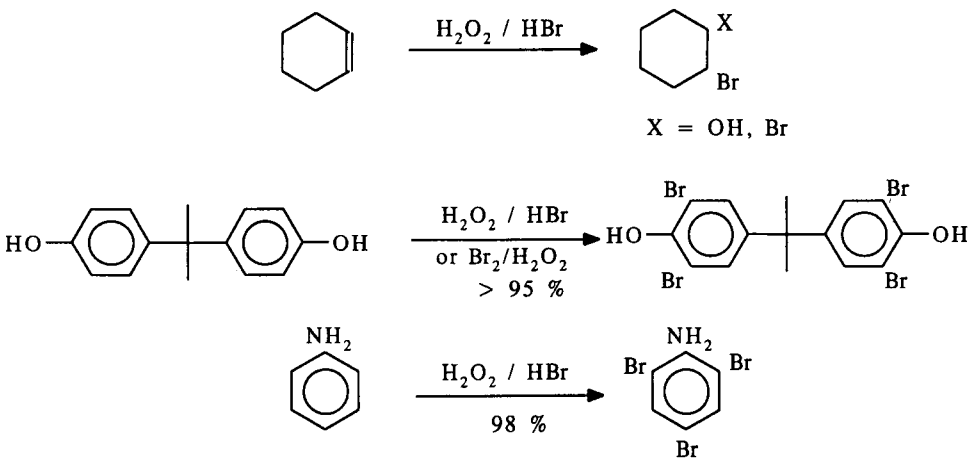
The fact that H_2O_2 reacts efficiently with halogen acids to generate the halogen in situ, can be used to good effect in bromination chemistry (ref. 2). Two approaches can be envisaged and both are used commercially. Firstly, one can carry out the bromination in the normal way adding bromine to the reaction. However, only half the 'normal' charge is added to complete half the reaction. At this stage H_2O_2 is added to regenerate bromine from the by-product HBr which has been produced and complete the reaction.

Alternatively, all the bromine can be generated from H_2O_2 but adding HBr at the start of the reaction instead of bromine. In both cases the bromine is fully utilised and thus bromide effluent is minimised. (Scheme 1).



Scheme 1. Use of H_2O_2 to recycle HBr

A number of examples could be used to illustrate the concept (ref. 2); a selection are shown below.



In the first example the product from the reaction can be controlled by choice of reaction conditions. Low temperatures and concentrated HBr give the dibromo products whilst high temperatures and lower concentrations of HBr favour the bromohydrin. Treatment of the latter intermediate with alkali gives the epoxide (ref. 3).

Aromatic bromination is also achieved in high yields for a variety of substrates including phenols (ref. 4) and anilines (ref. 5).

The same principle can be applied to chlorinations and iodinations (ref. 2) as well as to the benzylic bromination of toluenes and related substrates as intermediates to benzaldehydes and benzoic acids (ref. 6).

Whilst this process is attractive in that it removes an effluent problem and fully utilises the bromine used, it must be recognised that for some reactions, particularly where there is a degree of water sensitivity, the approach will not be practicable.

In these cases we must look for a method of curing the effluent problems and once again H_2O_2 offers a competitive advantage.

Recovery of Bromine using H_2O_2

A number of reagents / methods can be envisaged for recovering bromide from the waste streams of bromination processes.

These include chlorine, chlorate, Brocat (air) and H_2O_2.

Chlorine is used to obtain bromine from salt sources in primary production and is an excellent process for such large scale operations. For smaller scale recovery operations it is cheap in reagent terms but requires specialised equipment for handling and use which adversely impact on the process economics. Additionally, large volumes of salt are produced, creating a similar effluent problem to that which it is solving.

Chlorate can be used and will reduce the chloride loading of the final effluent compared to chlorine but it has disadvantages in terms of cost and handling (solid versus liquids) and has not been proven on an industrial scale.

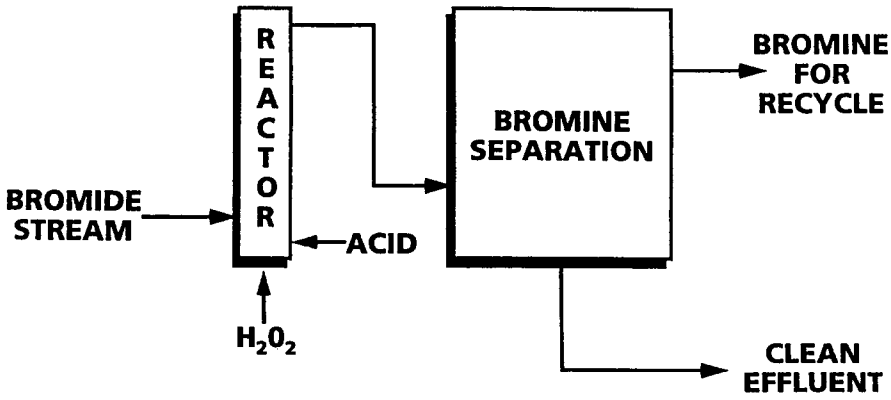
Catalytica (ref. 7) have reported a recovery process based on air and catalyst. Whilst the reagent is cheap, the process requires high capital investment. It is a clean process but only treats hydrogen bromide streams and cannot treat inorganic bromide streams directly.

Hydrogen Peroxide offers a clean, cost effective approach.

As already mentioned, H_2O_2 reacts rapidly with HBr to give a good yield of bromine (ref. 1). The reaction between 50 % H_2O_2 and 48 % HBr has been shown to be complete in less than 40 seconds and to give a bromine yield of > 95 %. The reaction is highly exothermic (25 Kcal per mole H_2O_2). These facts make the recovery of bromine from effluent with H_2O_2 a simple process.

The process can be adapted to handle all concentrations of bromide in the effluent, whether present as hydrobromic acid or salts. The controlling parameter is pH which must be maintained in the acidic region to enable the process to operate. This is most easily achieved using a mineral acid such as sulphuric acid to adjust the pH.

The schematic diagram of the equipment is shown below (Scheme 2).



The reactor can have a number of designs depending on individual requirements but in general both stirred tank and packed column reactors are viable, glass is the normal material of construction. After leaving the reactor, the bromine is separated from the aqueous solution and purified by standard techniques to get reagent ready for recycle into the process. Having removed bromide from the effluent stream and only added water and a small amount of sulphate, the final effluent is much cleaner.

It is known (ref. 8) that H_2O_2 will react with bromine to decompose the peroxide to oxygen and water.

$$3\,H_2O_2 + Br_2 \longrightarrow 2\,HBr + 2\,H_2O + 2\,O_2$$

However, this has very little detrimental effect on the process as the half life for this reaction at 40°C is 25 minutes, compared with the H_2O_2/HBr reaction time of 40 seconds.

In terms of economics, it has been calculated that the capital cost requirement for a unit to recover bromine by this method is relatively low. Consideration of the operating costs shows that the cost of recovered bromine using this process is about 30 % of that for purchasing new bromine. This takes no account of the savings associated with not having to dispose of the bromide.

ALTERNATIVE BROMINE RECOVERY METHODS COMPARED

As can be seen from the above information, H_2O_2 offers an attractive option for recovering bromine from waste streams. The alternative options can be compared qualitatively.

The four main options are :

- H_2O_2
- Chlorine
- Chlorate
- Brocat

The first comparison is that of costs. In general, operating costs will be similar for all options. The capital requirement for Brocat is particularly high, the others are similar. In terms of reagent costs Brocat (air) and chlorine are the cheaper.

We should also compare the scope of the technologies for different waste streams. With the exception of Brocat which only handles HBr, the systems can be used with HBr or metal salt streams. However, H_2O_2 has an advantage in terms of handling impurities in the steam such as low levels of organics. Chlorine and chlorate will suffer from reduced efficiency due to side reactions; Brocat has potential problems with catalyst poisoning. H_2O_2 suffers no major drawbacks in this respect.

In terms of handling the oxidant both air and H_2O_2 are much more easily handled than chlorine or chlorate on a small industrial scale.

The final effluent from the H_2O_2 process is basically clean whereas the chlorine based oxidants impart high chloride levels to the stream.

Finally from a safety view point H_2O_2 again has advantages over the chlorine based oxidants.

In summary, H_2O_2 has no major drawbacks. Chlorine is a good system but has a number of less favourable attributes; chlorate improves on some of these but a major problem is the need to handle solid. The Brocat system is capital intensive and therefore less flexible at lower volumes of effluent. It also cannot deal with salt solution directly.

SUMMARY

Manufacturers of brominated products are facing increasing economic, environmental and legislative pressure to improve their processing with respect to the effluent discharged.

Hydrogen peroxide offers a portfolio of potential solutions to prevent or cure the problems based on the high environmental acceptability of the reagent. The solutions are :

- Cost effective
- Simple
- Clean

ACKNOWLEDGEMENT

The efforts of other Solvay Interox personnel including, S.E. Blackett, S.C. Oakes, D. Pyke and S. L. Wilson, in developing this technology are gratefully acknowledged.

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BEHAVIOUR AND FATE OF AROMATIC BROMINE COMPOUNDS IN THE ENVIRONMENT

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ABSTRACT

Incineration of a collection of polymers with 10 different kinds of brominated flame retardants has been studied under standardized laboratory conditions using varying parameters including temperature and air flow. Polybrominated diphenyl ethers like the deca-, octa-, and pentabromo compounds yield a mixture of brominated dibenzofurans while burning in polymeric matrices. Besides cyclization, debromination/hydrogenation is observed. Influence of matrix effects and burning conditions on product pattern has been studied the relevant mechanisms have been proposed and the toxicological relevance is discussed.

The fate of aromatic bromine compounds such as brominated dibenzodioxins occurring on fly ash of municipal waste incinerators has been deduced from appropriate laboratory experiments. Stereoselective, first order ipso-substitution of bromine by chlorine is observed.

Photochemical degradation of brominated dibenzodioxins and furans has been studied. Decay of these compounds under environmental conditions is much faster compared to the chlorine analogues due to the higher values for the quantum yields of the bromine compounds.

INTRODUCTION

Aromatic and aliphatic bromine compounds play an important role as industrial products, e.g. special products are widely used as flame retardants for polymeric materials (ref. 1). Because there is an increasing interest and concern about the behaviour and fate of anthropogenic compounds in the environment (ref. 2), we have studied the physical behaviour and chemical reactivity of these products which are relevant to the environment. The main object is the study of their thermal behaviour during incineration, as well as photolytic reactions. Of prime concern is

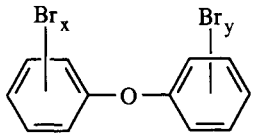
the question of formation and destruction of polybrominated dibenzodioxins (PBDD) and -furans (PBDF), which might be formed in various thermal processes. Since brominated dibenzodioxins and -furans show a similar toxicity compared to their chlorinated analogues (ref. 3), 8 PBDD/Fs have been defined as hazardous chemicals by German federal laws (Dioxin-Verordnung as part of Gef Stoff V) (ref. 4). Our studies can be applied to risk assessment of these products and may lead to subsequent legislative actions (ref. 5). These were two preliminary studies performed in 1986/87 (refs. 6,7) ; this review will cover our more recent results.

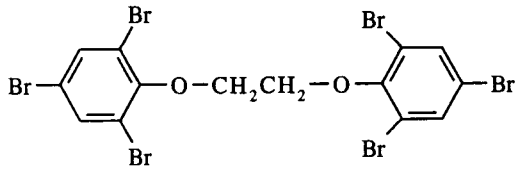
RESULTS AND DISCUSSION

1. Study of the Thermal Behaviour of Bromine Containing Flame Retardants during Incineration

The following 10 bromine compounds were investigated, in general within their polymeric matrices (see Scheme 1);

decabromobiphenyl ether **1**
octabromobiphenyl ether **2**
pentabromobiphenyl ether **3**
1,2-Bis(2,4,6-tribromophenoxy) ethane **4**
tetrabromobisphenol A **5**
tetrabromophtalic anhydride **6**
polybrominated styrene **7**
dibromopropyldian **8**
1,2-Bis (tetrabromophtalimide) **9**
hexabromocyclododecane **10**





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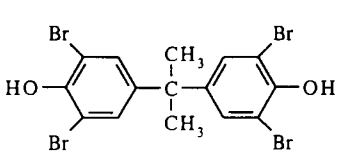
1, x + y = 10
2 x + y = 8
3, x + y = 5



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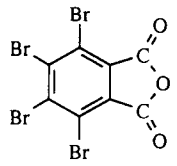

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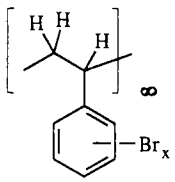

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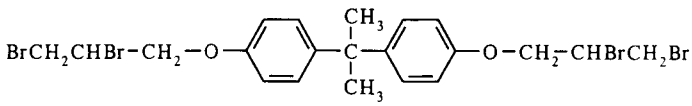

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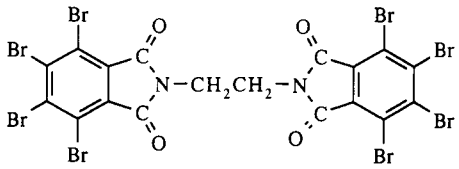

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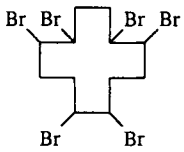

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Scheme 1. Structure of Investigated Brominated Flame Retardants

The following polymeric materials (commercial products) were investigated :

a) polystyrene with 10 % of **1** and 4 % Sb_2O_3;
b) polystyrene with 12,5 % of **1** and 4 % Sb_2O_3:
c) ABS with 14 % of **2** and 6 % Sb_2O_3;
d) polyurethane with 25,4 % of **3**;
e) ABS with 18 % of **4** and 7 % Sb_2O_3;
f) epoxilaminate with **5**;
g) epoxilaminate with **5** (other product);
h) epoxilaminate with copper-laminated **5**;
i) polybutylene-terephtalate with **5**;
j) polycarbonate with 12 % of **5**;
k) polyurethane with 33 % of **6**;
l) polyurethane with 6,4 % of **6**;
m) polyester with **7**;
n) polyester with **7** (other sample);
o) polypropylene with 5,9 % of **8**;
p) ABS with 11 % of **9**;
q) polystyrene with 3 % of **10**;

For bromoethers **1**-**3** several other polymeric matrices were also used; see below.

Incinerations were performed with the following three furnaces (Fig. 1-3) :

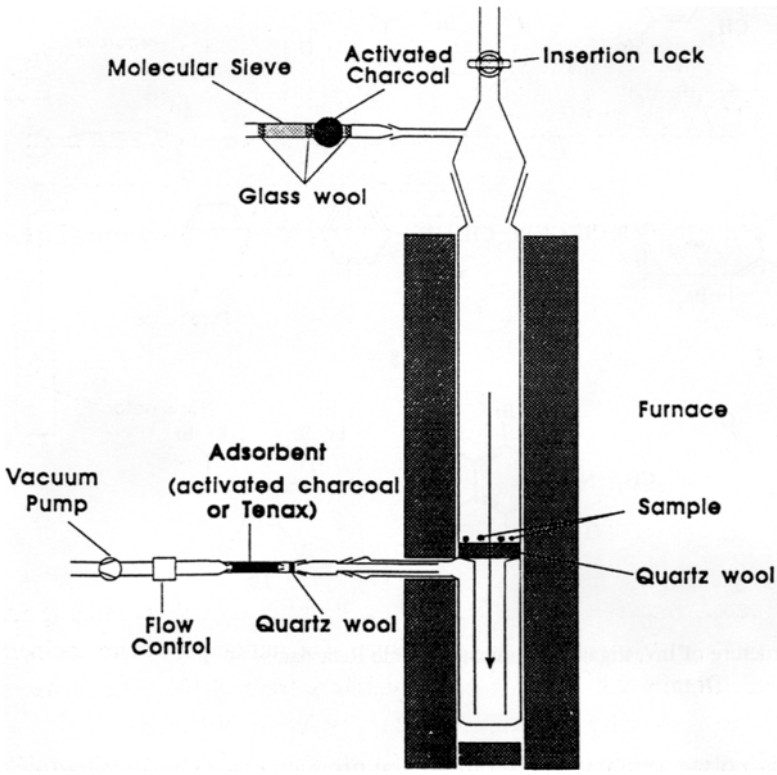


Fig. 1. VCI Apparatus (Furnace of Verband der Chemischen Industrie)

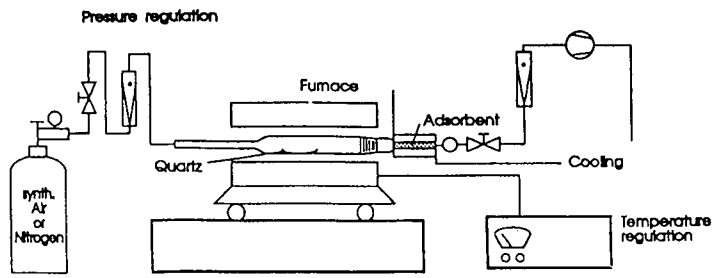


Fig. 2. BIS Apparatus (developed by Bayer, ICI, Shell)

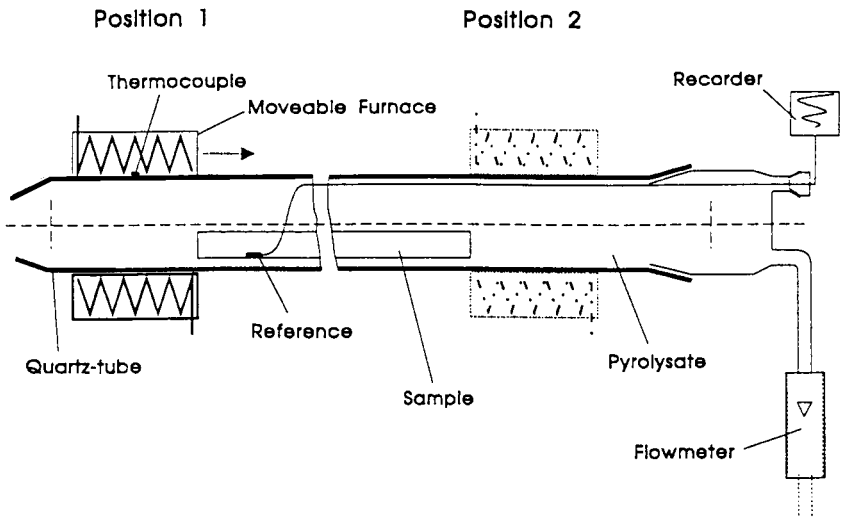
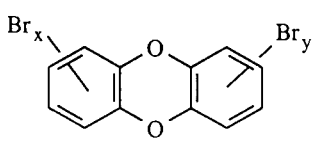


Fig. 3. DIN Apparatus (DIN No. 534336)

By variation of temperature and air flow rate burning conditions ranging form a smoldering fire to an open fire (e.g. conditions of a municipal waste incinerator) can be modeled. Details can be found in the literature (refs. 8-10). The furnaces are complementary to each other. In general similar results are obtained.

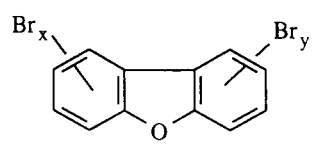
Special clean-up procedures were developed for PBDD/F in the pyrolysis products formed in either furnace; for incineration products of the VCI oven the following clean-up procedure was developed (ref. 11), see Scheme 1.

For the relevant structures of PBDD/F, see Figure 4.



x + y = 1 - 8

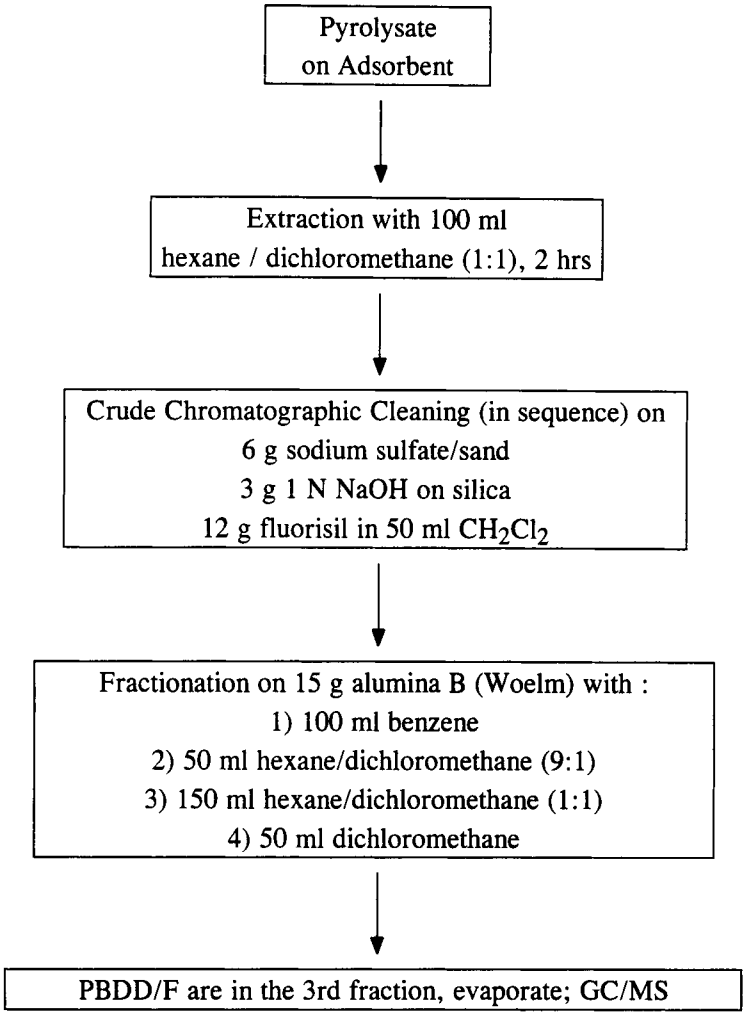
75 isomers



x + y = 1 - 8

135 isomers

Fig. 4. Structures of Brominated Dibenzodioxins and -furans



Scheme 1. Clean-up Procedure for PBDD/F in Pyrolysate of the VCI-Furnace

For details of the clean-up of the pyrolysate of the DIN oven see reference 12. Identification and quantification of PBDD/F was performed by GC/MS (refs. 8-12). This was done for all brominated PBDD and PBDF from mono- through octabromo compounds using external standards which were either prepared (refs. 11-13) or purchased. There exists a total of 210 brominated compounds of PBDD/F. Since not all isomers are available a complete isomer-specific determination could not be performed.

The following results have been obtained in the incineration studies. Polymers containing bromine compounds **4** and **5** yield PBDD/F in the ppm range (refs. 9,11,12). Incineration of compound **5** gives PBDD isomers but no toxic isomers (ref. 11). Polymers containing bromine compounds **6**-**10** do not yield any PBDD/F (refs. 9,12). Polymers containing brominated diphenyl ethers **1**-**3** however, yield PBDF during incineration in very high yield (refs. 9,10) ; depending on the applied conditions the conversion can be nearly quantitative. Therefore, this class of compounds was investigated more thoroughly (refs. 14,16).

First, thermal behaviour of decabromobiphenyl ether **1** will be described. The thermal reactivity of this compound depends on the applied conditions; the pure compound reacts completely different in comparison to its reaction in polymeric matrices. Thermolysis of the pure compound gives a good yield (60 %) of hexabromobenzene. The main products obtained by incineration in th DIN oven at three temperatures for pure **1** and of **1** within a polypropylene matrix are shown in Table 1.

Table 1. Main Products obtained by Incineration of Decabromobiphenyl ether **1** at three Different Temperatures; Yields are in Percent by Weight (ref. 12)

Product	400°C	600°C	800°C
1	22,3[a] ; nd[b]	nd[a] ; nd[b]	nd[a] ; nd[b]
hexabromobenzene	12,3[a] ; nd[b]	56,8[a] ; nd[a]	0,6[a] ; nd[ab]
PBDD/F	0,08[a] ; 25,5[b]	0,3[a] ; 12,4[b]	0,2[a] ; 5,5[b]
CO_2	4,5[a] ; 3,0[b]	9,9[a] ; 3,5[b]	16,3[a] ; 4,3[b]
HBr	nd[a] ; nd[b]	nd[a] ; 1,0[b]	nd[a] ; 2,2[b]
Br_2	nd[a] ; nd[b]	9,4[a] ; nd[b]	10,9[a] ; nd[b]

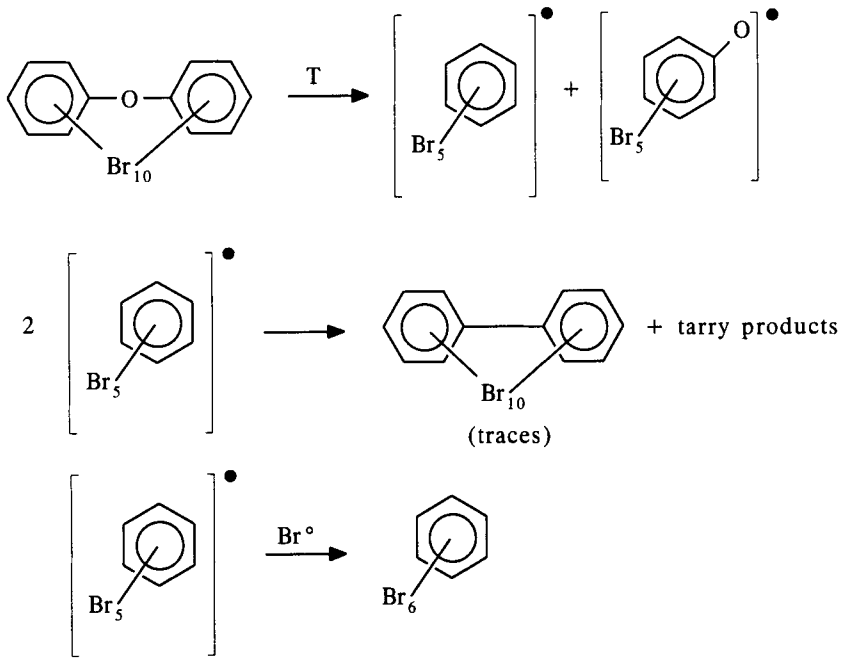
a from pure compound **1**;

b from compound **1** with the polymeric matrix (polypropylene and 4 % Sb_2O_3)

nd; not detected within the detection limit (< 0,1 %)

The determined products do not add to 100 % since insoluble tarry products are also obtained. A similar product mixture is obtained by heating compound **1** in a sealed ampoule to 600°C (ref. 12). These results show that the thermochemistry of **1** depends strongly on whether it is performed with pure compound **1** or if **1** is heated within a polymeric matrix.

For the thermochemistry of pure decabromobiphenyl ether, the following mechanistic scheme has been suggested (Scheme 2) (ref. 11).

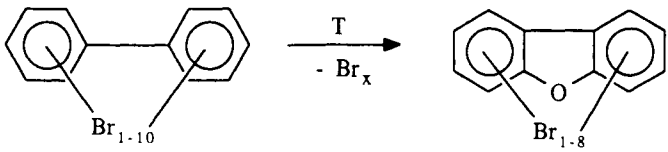


Scheme 2. Proposed Mechanism for Thermolysis of Pure Decabromobiphenyl Ether (1)

First the carbon oxygen bond is cleared homolytically. The pentabromophenyl radical can either react with itself yielding polymeric, tarry products or it is trapped by a bromine atom.

Since the yield of hexabromobenzene from bromoether **1** is in the range of 60 %, this thermolytic reaction can be used for preparative purposes.

Thermochemistry in the polymeric matrix follows a different pattern. Decabromobiphenyl ether **1** does cyclize according to the following reaction yielding brominated dibenzofurans (PBDF). The optimal yield for PBDF depends on the applied burning temperature (refs. 14,15) ; this itself depends on the kind of polymeric matrix, which is shown below for incineration at the DIN-oven (Fig. 5).



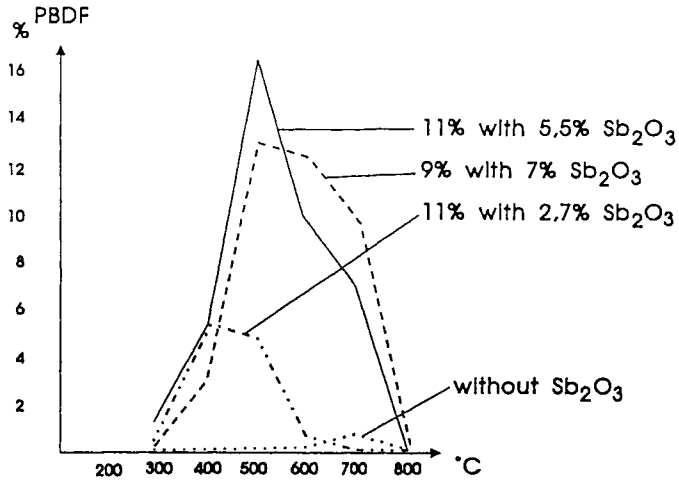


Fig. 5. Yields of Brominated Dibenzofurans from Decabromobiphenyl Ether as Dependent on Temperature and Amount of Sb_2O_3 (Synergist) in the Polymeric Matrix (Polybutylene-terephtalate).

It can be seen from Figure 5 that the amount of the added synergist Sb_2O_3 of the flame retardant strongly effects the PBDF yield and the optimal temperature of PBDF formation. The kind of polymeric matrix itself does not effect yields of PBDF.

During incineration of **1** in the polymeric matrix debromination/hydrogenation occur in addition to cyclization process. Tetrabrominated dibenzofuran isomers are the most abundant products formed in the temperature range between 300° or 400° (Figure 6 shows Br-composition at 300° - 800°C). Incineration at 400°C gives tetrabromo-benzofurans in yields up to 13 % (Fig. 6). Besides of PBDF, brominated dibenzodioxins are also formed, but to a much lesser extent (30-90 ppm) (ref. 11).

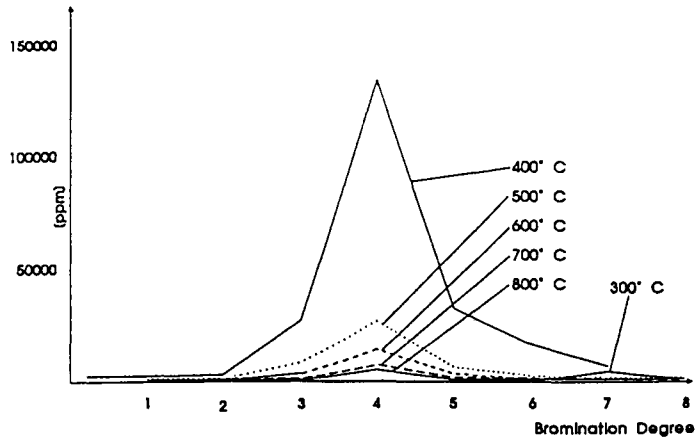


Fig. 6. Yield and Distribution Pattern of PBDF formed from Incineration of Decabromodiphenyl Ether in Polybutyleneterephtalate with 5,5 % Sb_2O_3 at 6 different Temperatures.

It can be seen from Figure 6 that tetrabrominated dibenzofurans dominate at all temperatures used for incineration. The toxic 2,3,7,8-isomer has been detected as part of the mixture and estimated at nearly 2 % of the total PBDF (ref. 12).

Similar results are obtained from incineration of polymeric materials with octabromo- and pentabromodiphenyl ether (refs. 11,12). The temperature with the maximum PBDF-yield depends on the kind of polymeric matrix. All three bromo ethers 1-3 give the same isomer distribution pattern with preference for tetrabrominated dibenzofurans. The overall yield of PBDF is lower for incineration of pentabromobiphenyl ether **3**, 4 % at 700°C compared to 29 % for ether **1** at 500°C (ref. 12). The preferred formation of tetrabrominated furans observed at all temperatures cannot be a result of thermodynamic control of the cyclisation reaction; it is likely due to the special geometry of the furnaces. One explanation is that a spontaneous reaction occurs at approximately 400°C while the pyrolysis products are transferred to the cooler zones of the reactor; details can be found elsewhere (ref. 12).

The influence of metal species like copper has been investigated on the product pattern and yield of PBDD/F (Fig. 7) (ref. 11). This study is relevant to accidental fires of polymeric materials of electronic devices which are associated with various metals like copper. As a result of the presence of the metal species substantial amounts of both PBDF and PBDD are formed.

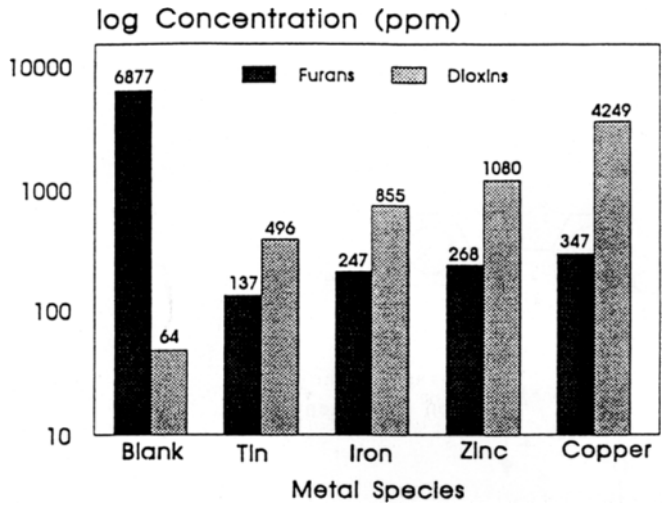
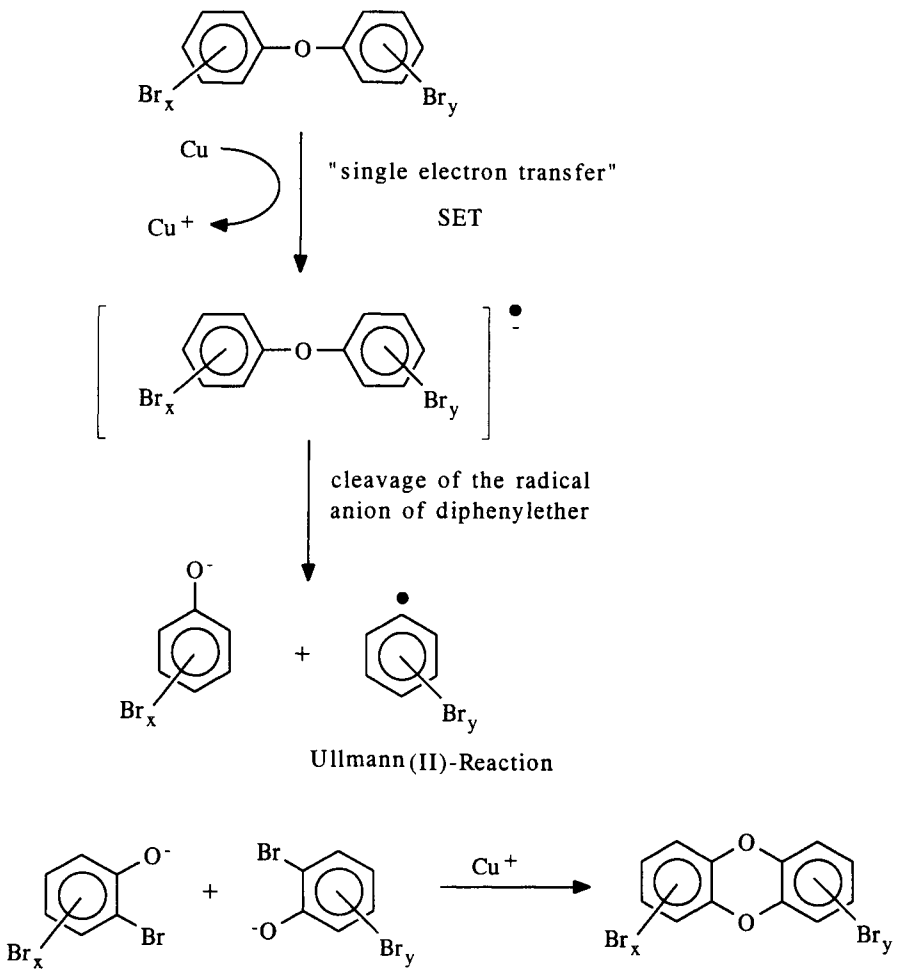


Fig. 7. Influence of Various Metal Species on PBDD/F Concentrations during Incineration of Decabromobiphenyl ether in Polybutyleneterephtalate at 500°C (BIS-Furnace).

The additional formation of PBDD from brominated diphenylether can be explained by a SET mechanism, see Scheme 3.



Scheme 3. Mechanism of Copper Catalyzed Formation of PBDD from Polybrominated Diphenyl Ethers.

This scheme is selfexplanatory. Important in the formation of PBDD by Ullmann reaction of brominated phenoxy radicals. Influences of added water, air content and other factors on PBDD/F yield and pattern have also been studied in detail (ref. 11).

The presence of metal oxides have a different influence on PBDD/F concentration and pattern (ref. 11), see Figure 8. Oxides of zinc and copper reduce the PBDD/F yields due to debromination reactions. The two oxides of copper show

a distinctively different effect, while CuO leads to a strong reduction of PBD/F yield Cu_2O_2 enhances the PBDD concentration by the SET mechanism.

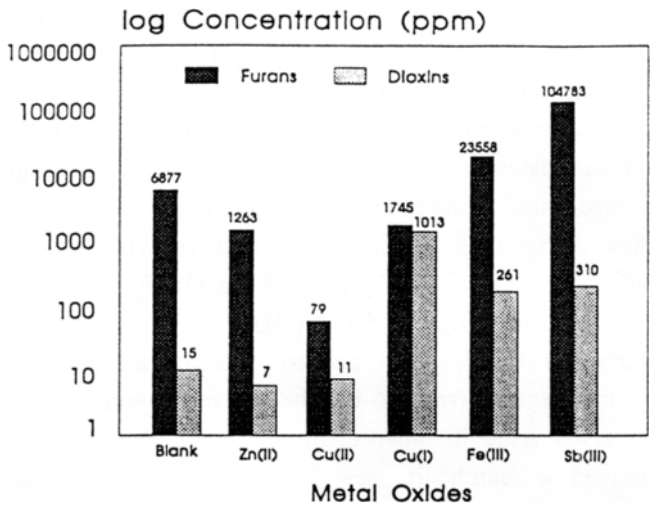
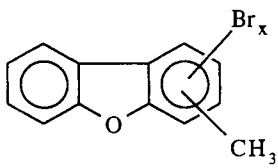
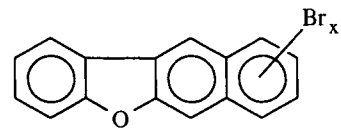


Fig. 8. Influence of Various Metal Oxides on PBDD/F Concentrations during Incineration of Decabromobiphenyl ether in Polybutyleneterephthalate at 500°C (BIS-Furnace).

Besides these main products, formed in incineration of **1** in polymeric matrices complex isomeric mixtures of brominated methyl-dibenzofurans and brominated condensed systems like benzo[b]naphto[2,3-d]furan have been identified by GC/MS (ref. 11).



Brominated Methylbenzofurans



Brominated Benzo[b]naphto[2,3-d]furans

It is possible that brominated dibenzodioxins and -furans are formed in trace levels during the preparation of technical bromoether products **1-3**. Dumler (ref. 12) and others (ref. 17) have found PBDD/F in the ppm range in commercial samples of decabromodiphenyl ether. A more recent and advanced study has been

performed on currently manufactured technical products of bromoethers **1-3**; none of the 15 toxic PBDD/F with the 2,3,7,8-pattern (the octabromo compounds were excluded) were detected within the detection limit (0.1 ng/kg) (ref. 18).

It was shown above that formation of PBDF from decabromobiphenyl ether **1** occurs even in the temperature range of 250-300°C. Therefore there exists a chance that formation of these compounds starts during the technical extrusion process (mixing the polymeric material with the flame retardant). The concentration of PBDD/F in the plastic materials has been measured at these temperatures in a pilot plan test. PBDF were found in the resin blend in the range of 1-560 ppb as well as in the surrounding ambient air of the working place. High concentrations of PBDD/F were measured in the air; e.g. 34 ng/m^3 for TBDF; 143 ng/m^3 for PBDF; 554 ng/m^3 for HBDF; 200 ng/m^3 for HpBDF, besides smaller amounts of brominated dibenzodioxins (ref. 19). The results mentioned above have lead to legislative actions in Germany (ref. 5), but the use of brominated diphenyl ethers remains a controversial issue in other countries (ref. 20). The impact of these results also prompted a search for new flame retardant duroplastic materials containing no halogen for electronic devices (ref. 21).

2. Fate of Aromatic Bromine Compounds During Municipal Waste Incineration

Aromatic bromine compounds can be formed and transformed during various thermal processes, like aromatic chlorine compounds (ref. 22). Brominated dibenzodioxins and -furans and mixed brominated/chlorinated compounds have been detected in trace levels in the fly ash of a municipal waste incinerator (ref. 23).Chlorine is generally abundant compared to the bromine of typical municipal waste; the chlorine vs. bromine ratio is in the range of 250:1.

We have simulated the relevant reactions occurring at 300°C on the surface of fly ash of electrostatic filters of a municipal waste incinerator (MWI) using the following device (Fig. 9) (ref. 24).

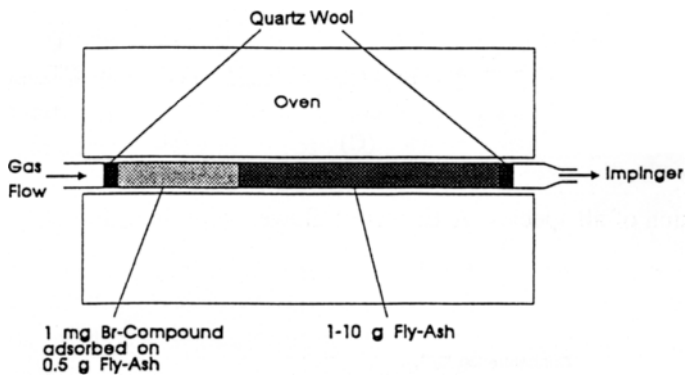


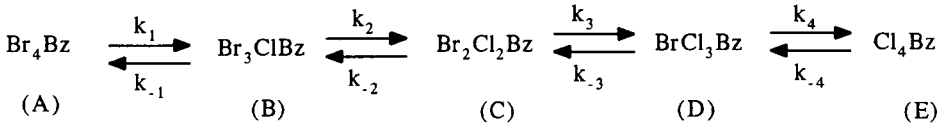
Fig. 9. Schematic Drawing of the Apparatus for the Study of Aromatic Bromine Compounds on Fly-ash.

The chlorine content of the fly ash is 4.9 %, the bromine content 0.065 %. A series of brominated aromatic compounds has been adsorbed on this fly ash and treated for 1 h. with air at 300°C. The extraction and analysis yield mixed brominated/chlorinated as well as completely chlorinated products. This is shown for 5 aromatic bromine compounds in Table 2.

Table 2. Formation of mixed brominated/chlorinated and completely chlorinated products by reaction of brominated compounds on 3.5 g of fly ash at 300°C in as stream of dry air.

Brominated Compounds	Yield of Completely Chlorinated Compound (%)	Yield of Mixed Brom./chlor. Compounds (%)	Recovery (%)
1,2,4,5-Tetrabromobenzene	13.3	45.8	64.4
Hexabromobenzene	27.9	56.9	87.5
2,3,7-Tribromodibenzodioxin	21.5	23.9	54.8
1,2,3,4-Tetrabromodibenzodioxin	36.1	5.1	41.9
Decabromophenyl ether	85.1	6.4	91.5

To elucidate the mechanism of the reaction transhalogenation of 1,2,4,5-tetrabromobenzene (Br_4-Bz) was investigated in detail. Subsequent halogen exchange yields tetrachlorobenzene (Cl_4-Bz) via the three intermediates B, C and D.



Concentration of all species, A-E, were followed with time (Fig. 10).

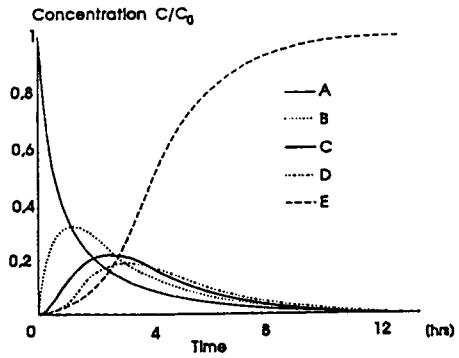
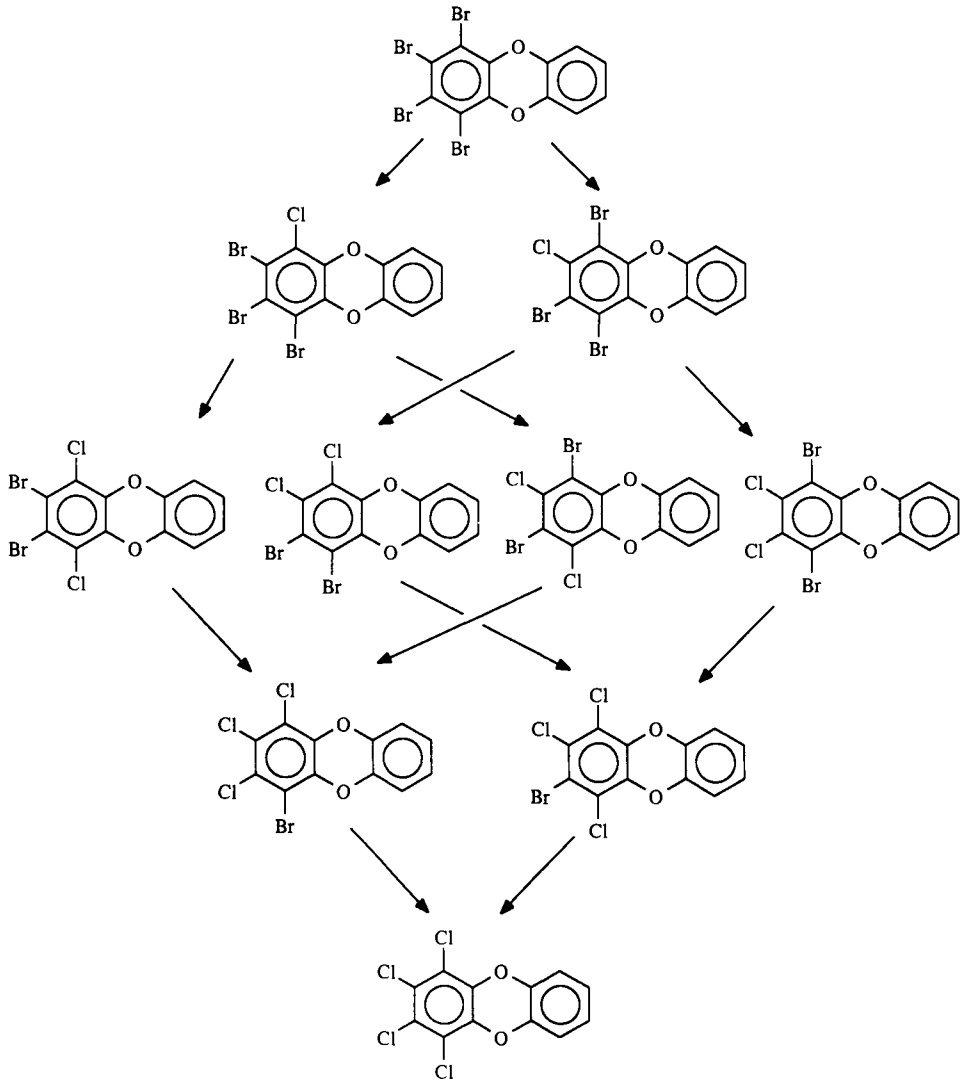


Fig. 10. Concentration curves fitted by exponential regression for the reaction of 1,2,4,5-tetrabromobenzene (A) with surface bound chloride, a consecutive four-stage reaction with three intermediates (B,C,D) and the product E.

Since chlorine is always in more than a hundred-fold excess compared to bromine the reaction is occurring by pseudo monomolecular kinetics. The reaction occurs via nucleophilic aromatic substitution by an addition-elimination mechanism, the so-called S_{NAr} mechanism (ref. 24).

Stereochemistry of the halogenation-dehalogenation reaction was studied for 1,2,3,4-tetrabromodibenzodioxin, TBDD (Scheme 4).



Scheme 4. Isomeric specific Reaction Pattern of the Halogenation-dehalogenation of 1,2,3,4-Tetrabromodibenzodioxin on the Surface of Fly-Ash.

All products were identified and followed by GC/MS. The lateral positions (C-2, C-3) of 1,2,3,4-TBDD are slightly more reactive compared to the peri positions (C-1, C-4); the two Br_3Cl-isomers appear in a ratio of approximately 1:1,5. The relative rate constants of 5 aromatic bromine compounds were determined (Table 3).

Table 3. Relative rate constants (K_{rel}) and half lifes ($t_{1/2}$) for a mixture of aromatic bromine compounds calculated from the concentrations of educts after reaction with 3.5 g fly ash containing chlorine.

Compound	Rel Concentration (%)	K_{rel}	$t_{1/2\ (rel)}$
1,2,4,5-Tetrabromobenzene	8.2	1	1
Hexabromobenzene	3.1	1.3	0.8
2,3,7-Tribromodibenzodioxin	17.2	0.6	1.6
1,2,3,4-Tetrabromodibenzodioxin	1.7	1.5	0.7
Decabromodiphenyl ether	< 0.1	> 2.5	< 0.4

The difference in reactivity is not as much as is generally observed in nucleophilic aromatic substitution in solution by an addition-elimination mechanism (ref. 25). Substituents with electron withdrawing capabilities enhance the rate of the reaction; therefore decabromobiphenyl ether reacts nearly 2 times faster than 1,2,3,4-tetrabromodibenzodioxin.

These results show the fate of aromatic bromine compounds during municipal waste incineration : bromine is exchanged by chlorine on the surface of fly ash at the electrostatic precipitator at 250-300°C. But the toxic potential at brominated dibenzodioxins and furans is not reduced by these transformations. The increase of PCDD/F concentration in MWI by adding bromine compounds has been pointed out by Lahl and coworkers (ref. 26).

3. Photochemical Degradation of Brominated Dibenzodioxins and Furans

Photochemical decay of PBDD/F is a possible sink for these micropollutants. Therefore, we have studied the photochemistry of these compounds in two solvents; n-hexane and methanol (ref. 27). A similar study has been performed by Buser (ref. 28).

Photolysis of all brominated dibenzodioxins investigated occurs very fast in n-hexane. The rate of degradation of all compounds follows a good first-order kinetic scheme. In Table 4 the calculated first order rate constants k are summarised along with the quantum-yields. The corresponding results for three brominated dibenzofurans are also included.

Table 4. Photolysis constants (k) and Quantum Yields (Φ) of Brominated Dibenzodioxins and -furans in n-Hexane as Solvent. A and B are replicates.

Compound	k (s^{-1})	Φ (mol $einst^{-1}$)
MonoBrDD	$4.46 \times 10^{-3} \pm 6.72 \times 10^{-4}$	0.14 ± 0.02
2,7/2,8-DiBrDD	$5.65 \times 10^{-3} \pm 1.01 \times 10^{-3}$	0.14 ± 0.002
2,3,7-TriBrDD	$7.26 \times 10^{-3} \pm 1.33 \times 10^{-3}$	0.45 ± 0.08
1,2,3,4-TetraBrDD (A)	$5.04 \times 10^{-3} \pm 3.38 \times 10^{-4}$	0.21 ± 0.01
1,2,3,4-TetraBrDD (B)	$5.94 \times 10^{-3} \pm 1.24 \times 10^{-3}$	0.18 ± 0.04
1,2,3,7,8-PentaBrDD	$1.22 \times 10^{-2} \pm 3.70 \times 10^{-4}$	0.45 ± 0.01
1,2,4,7,8-PentaBrDD	$1.15 \times 10^{-2} \pm 1.05 \times 10^{-3}$	0.42 ± 0.04
1,2,3,4,7,8-HexaBrDD	$1.55 \times 10^{-2} \pm 1.37 \times 10^{-3}$	0.53 ± 0.05
OctaBrDD	$7.73 \times 10^{-3} \pm 1.51 \times 10^{-3}$	0.17 ± 0.03
2,8-DiBrDF		0.037
2,3,7,8-TetraBrDF	8.98×10^{-2}	
1,2,3,4,6,7,8-HeptaBrDF	8.28×10^{-2}	0.712

These experiments show that the rate constants generally increase with increasing numbers of bromine atoms.

The same trend is observed in the series of brominated dibenzofurans. But the rate for OctaBrDD does not follow this general pattern since its rate is decreased compared to the penta- and hexabrominated compounds.

The reaction products formed in the photolysis of all these brominated dibenzodioxins have been determined with dependence on time. In general, consecutive substitution of bromine by hydrogen does occur, this is shown below for photolysis of 1,2,3,4-TBDD (Fig. 11).

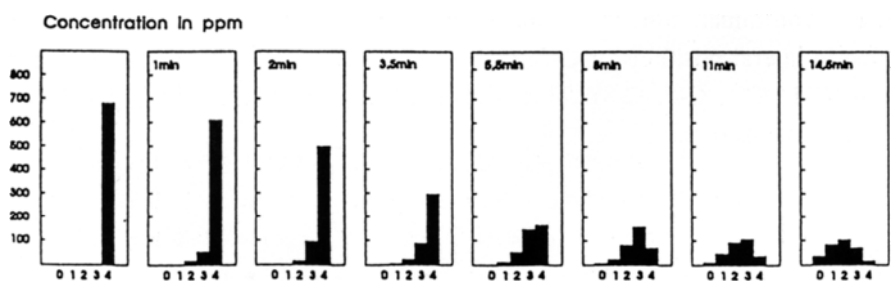
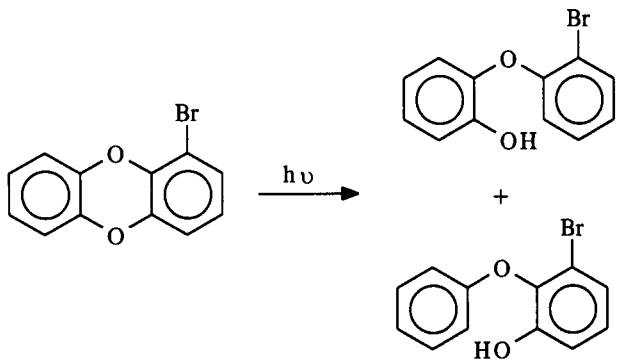


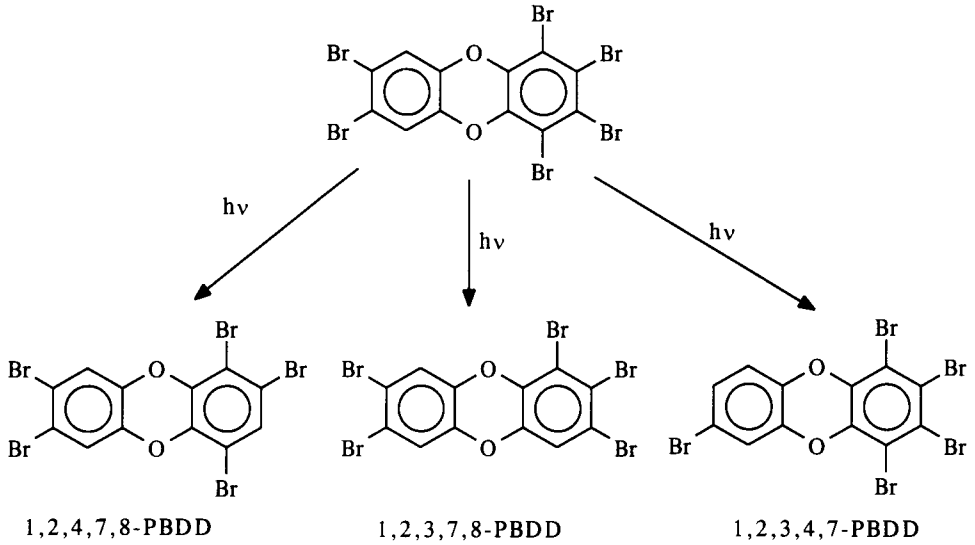
Fig. 11. Products formed from Photolysis of 1,2,3,4-TetraBrDD with increasing Time (in Hexane).

The reactions were followed by GC/MS. No debromination product accumulates during photolytic degradation in n-hexane of the higher brominated compounds : tetra- to octabrominated dibenzodioxins. The mass balance shows that in addition to the Br/H exchange some other reactions must occur. It is likely that unsubstituted dibenzodioxin can be degraded by photolysis in hexane to o-hydroxybenzoic acid. But other degradative pathways may also be responsible for the negative mass balance. Lower brominated dibenzodioxins like monoBrDD and diBrDD show a ring fission of one ether bridge; e.g.



This reaction has been also described for low chlorinated dibenzodioxins. Assuming an identical MS response factor for monoBrDD and monobromohydroxy-biphenyl ether (monoBrDPE) a quantification study shows that monoBrDPE is much more stable towards photolysis compared to monoBrDD, because it accumulates in the mixture of the reaction products. For the dibrominated dibenzodioxins the same reaction (ether fission) is observed but to a minor extent. With triBrDD and higher brominated BrDD no diaryl-ether products are observed at all.

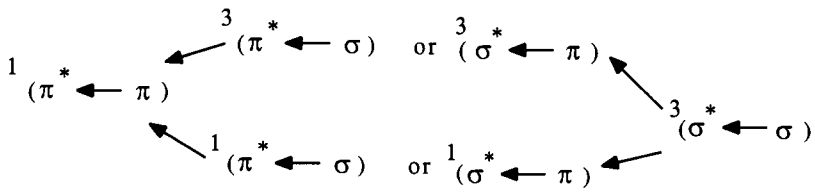
The debromination/hydrogenation reaction shows some stereospecificity. Bromine in lateral positions of C-2, C-3, C-6 and C-7 reacts faster than in the peri position (C-1, C-4, C-5, C-8). This is shown below for photolysis of 1,2,3,4,6,7-hexabromodibenzodioxin.



The three pentabromo isomers are observed after photolysis of 0,5 min in the ratio of 1:MO.48:0.01. After 14 min photolysis the relative ratio is 1:0.24:0.

Similar conclusions have been drawn for 1,2,3,4-BrDD by Buser (ref. 28).

The proposed mechanism of the reaction is shown below in Scheme 5.



Scheme 5. Proposed mechanism of the Photolytic Reaction of PBDD/F in Hexane

The primary step is the absorption of a quantum, which results in an excitation of the π-orbital. This singlet orbital can undergo intersystem crossing with spin change to a triplet stage (σ*,σ), which has been found in brominated arenes (ref. 29). The photolytic reaction in methanol is much slower compared to hexane (ref. 27). This is shown for 1,2,3,4-TBDD, for which the decay constants have been determined in both solvents :

$k = 9.5 \times 10^{-4}$ [sec^{-1}]; methanol

$k = 5.4 \times 10^{-3}$ [sec^{-1}]; n-hexane

A model for photolytic degradation of PBDD/F in the environment has been suggested by us (ref. 27).

4. Physical Properties of Brominated Dibenzodioxins

Some characteristic physical properties of PBDD/F have been determined and can be found elsewhere [8-14]. An important property for environmental behaviour is the vapour pressure. Vapour pressures of some PBDD has been measured by a special new technique [30] .Fig. 12 shows extrapolated vapour pressures of PCDD and PCDF and of corresponding PBDD and PBDF.

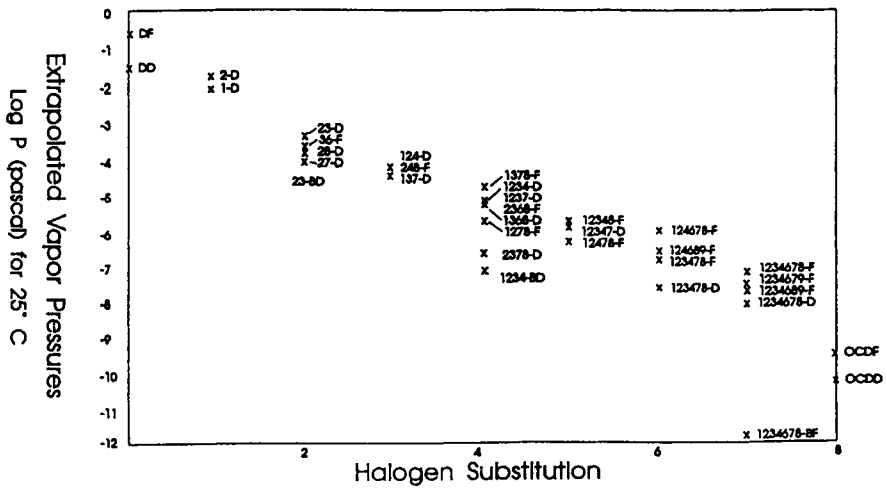


Fig. 12. Extrapolated Vapor Pressures of PCDD and PCDF and of corresponding PBDD and PBDF.

ACKNOWLEDGEMENTS

I thank Dr. Wayne Garrison, GSF Visiting Scientist from the Athens Environmental Research Laboratory, U.S.EPA, for suggestions and correction of the manuscript; the typing by F. Gillmeister is gratefully acknowledged.

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COMPARISON OF HEPATOTOXICITY OF MONOBROMOBENZENE, DIBROMOBENZENES, HEXABROMOBENZENE AND TETRABROMOBISPHENOL A

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SUMMARY

Monobromobenzene **1**, 1,2-dibromobenzene **2**, 1,3 dibromobenzene **3**, 1,4-dibromobenzene **4**, hexabromobenzene **5** and tetrabromobisphenol A **6** are used as plasticizers, flame retardants or intermediates for various syntheses. Except for **1**, a limited number of studies regarding the toxicity and metabolism of above compounds has been performed. This report presents some studies on the hepatotoxic action (necrotic and porphyrogenic effects) of these compounds.

Balb'c mice and Wistar rats were used in the experiments. The administration of single doses of **1**, **2** and **3** caused mainly necrotic changes in the liver, measured by GPT and histopathology. The extent of necrosis depended on doses and on time of observation (1-4 days after injections). In shorter time interval (2-4 hrs) **1**, **2** and **3** caused depletion of hepatic GSH (even up to 10 % of control). **4** and **5** did not generate necrotic changes. Increased GPT activity was observed after 3 doses of **6**. Single doses of **4**, **5** and **6** mostly increased the level of malondialdehyde (MDA-indicator of lipid peroxidation) in the liver. Repeated injections (3-7) of the investigated compounds enhanced the activity of ALA-D or ALA-S in the liver and caused steatosis.

Necrotic changes were characteristic of acute intoxication in mice, especially after single doses of **1**, **2** and **3**. Porphyrogenic effects appeared after repeated exposure to all studied compounds, mostly following dibromobenzenes and **5**.

INTRODUCTION

The brominated organic compounds are used as either additive (e.g. decabromodiphenyl, hexabromobenzene, pentabromotoluene), or reactive flame retardants (e.g. tetrabromobisphenol-A, tri- and pentabromophenols). The major

application of these compounds is in thermoplastic and thermoset resins, textiles and adhesives (ref. 1).

The use of aromatic brominated compounds as flame retardants has been a potential source of environmental contamination. Incomplete incineration of these compounds and wastes (plastics, textiles, oils etc...) containing brominated flame retardants caused formation of brominated/chlorinated dibenzodioxines (PBDDs/ PCDDs) and dibenzofurans (PCDFs/PBDFs) (refs. 1 - 4).

Brominated flame retardants and their metabolites are, for example, found in : water : (less than 0.1 μg/l), river sediments (≤ 20 μg/kg dry), fish (liver, fat. ≤ 20 μg/kg wet), seabirds (fat ≤ 350 μg/kg) and humans (fat. 0.1 - 4 μg/kg) (refs. 1,5-8).

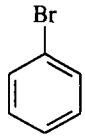
Except for polybrominated biphenyls (PBB), a limited number of studies regarding the toxicity of aromatic brominated compounds has been performed. Some experiments suggest a moderate acute toxicity of these compounds (ref. 1).

Potential hepatotoxic effects of various brominated benzenes, however, should be considered. Bromobenzene which is a monobrominated compound, is used in various experiments as a model hepatotoxic compound (refs. 9-11).

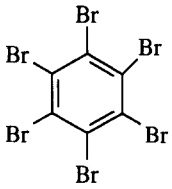
The purpose of this study was to compare hepatotoxic effects of monobromobenzene, 3 dibromobenzene isomers, hexabromobenzene and tetrabromobisphenol A; with special attention paid to the dynamics of changes of selected indicators of liver necrosis during acute poisoning.

MATERIALS AND METHODS

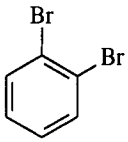
The experiments were performed on male Balb'c mice with body weight 23-30 g, and on male Wistar rats - body weight 190-250 g. The animals were fed with Standard LSM chow and given water ad libitum. The animals were administered oil solutions or suspensions of monobromobenzene **1**, 1,2-dibromobenzene **2**, 1,3-dibromobenzene **3**, 1,4-dibromobenzene **4**, hexabromobenzene **5** or tetrabromobisphenol A **6** (Fig. 1) in single or multiple doses (3-7 times), as presented in Table 1.



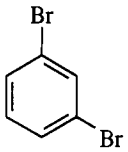
monobromobenzene **1**



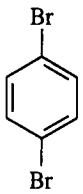
hexabromobenzene **5**



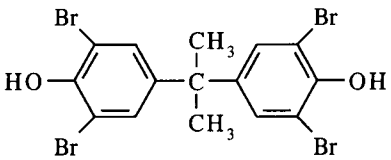
1,2-dibromobenzene **2**



1,3-dibromobenzene **3**



1,4-dibromobenzene **4**



Tetrabromobisphenol **6**

Fig. 1. The studied compounds.

Table 1. Doses of studied compounds

Compound	Animals	Route of administration	Number of doses	Range of doses [mg/kg]
1	mice	ip	1	200 - 800
	mice	ip	7	50
	rats	po	7	75 - 300
2, 3, 4	mice	ip	1	150 - 2200
	mice	ip	7	30 - 450
	rats	po	7	45 - 400
5	mice	ip	1	600 - 9000
	mice	ip	7	600
	rats	po	3 - 7	100 - 3000
6	rats	ip, po	1	500 - 1000
	rats	po	3 - 7	500 - 2250

ip - intraperitoneally
po - per os

The control animals had no injections, or where injected sunflower oil. During the experiment the animals were divided into groups of 4-6.

Sections and all measurements after a single dose were carried out after 2, 4, 12, 24, 48, 72 and 120 hours following injection of the compounds. In the case of 3-7 fold administration, the animals were sacrificed 24 hours after the last dose. Rats were sacrificed under ether narcosis, mice - by dislocation of the spinal cord. Then livers and blood from heart were collected.

Activities of glutamate-pyruvate transaminase (SGPT, GPT) (EC 2.6.1.2), L-γ -glutamyl-transferase (γ-GT) (EC 2.3.2.2) and level of triglycerides (TG) in serum, as well as levels of glutathione (GSH) and malondialdehyde (MDA) in the liver were determined.

GPT activity was determined by the colorimetric method with 2,4-dinitrophenyl-hydrazine (refs. 12,13). Results were calculated on the basis of the calibration prepared from pyruvate, made for each series of determinations. The amount of pyruvate ($\mu mol/cm^3$) formed during 1 h incubation at 37°C was assumed as the activity unit.

The glutathione (GSH) level was assayed by the method of Sedlak and Lindsay (ref. 14), using Ellman's reagent (5,5-dithio-bis-(2-nitrobenzoic acid). Calibration was carried out parallely to each series, using reduced glutathione as a standard.

Malondialdehyde (MDA) was determined with thiobarbituric acid as described by Mihara et al. (ref. 15). The absorbance of butanol phase containing the aldehyde was measured at 532 nm. Calculations were made using the extinction coefficient according to Casini et al. (ref. 16).

Gamma-glutamyl-transferase activity was determined according to "Monotest 10 γ-GT neu" from Boehringer-Mannheim.

The concentration of triglycerides was estimated with the use of "Triglycerides GPO-PAP High performance" from Boehringer-Mannheim.

5-Aminolaevulinate dehydratase (ALA-D) (EC 4.2.1.24) in mice and rats livers was determined after 7-fold administration of the studied compounds according to Berlin (ref. 17), as modified by Schlick et al. (ref. 18). 5-Aminolaevulinate synthase (ALA-S) (EC 2.3.1.37) was also assayed in the liver according to Sassa and Granick (ref. 19).

All results were evaluated using the Student t-test, at the 5 % level of statistical significance.

For light microscopic examination, liver tissue was fixed in 10 % buffered formalin, embedded in paraffin, sectioned and stained with hematoxylin and eosin. In some cases, preparations were stained with PTAH (phosphotungstic acid-haematoxylin), by the Van Gieson method and the PAS (periodic acid-Schiff)

reaction was performed, or they were stained with oil red (on frozen sections). The extent of necrosis was scored on arbitrary scale : 1, negative; 2, individual hepatocytes; 3, < 25 % of hepatocytes; 4, 25-50 % of hepatocytes; 5, > 50 % of hepatocytes.

RESULTS

A single administration of monobromobenzene or hexabromobenzene resulted in decreasing the level of reduced glutathione in mice liver; to an extent varying according to the applied compound and dose. Figure 2 presents the level of gluthatione after the administration of the highest doses of **5** and **1** (9000 mg 5/kg and 800 mg 1/kg). The maximum decrease in GSH level following **5** and **1** was, respectively, 35 % and 90 % with measurements made of 12 and 4 hours after administration.

The GSH level retained its control values after lower doses used in our experiments (200 and 400 mg 1/kg; 600, 1200 and 4500 mg 5/kg).

This considerable decrease of GSH level following **1** was accompanied by the increase of SGPT (GPT) activity in the serum and necrosis in the liver (Fig. 2). No such changes were noticed after injection of **5**.

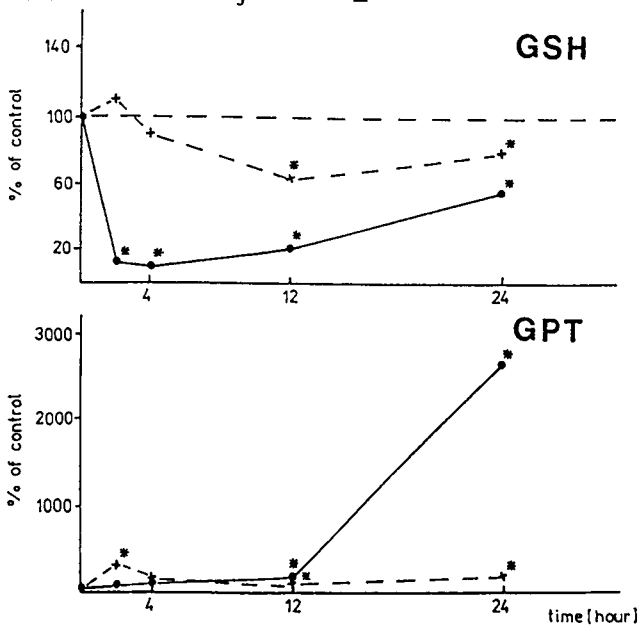


Fig. 2. The level of GSH in mice liver and the activity of GPT (SGPT) in serum after single administration of 800 mg BB/kg (——) and 9000 mg HBB/kg (x------x).
* - significantly different from control animals,
$\alpha = 0.05$

Both compounds resulted in statistically significant increase of MDA level in the liver (Fig. 3), which can exemplify lipid peroxidation in the liver.

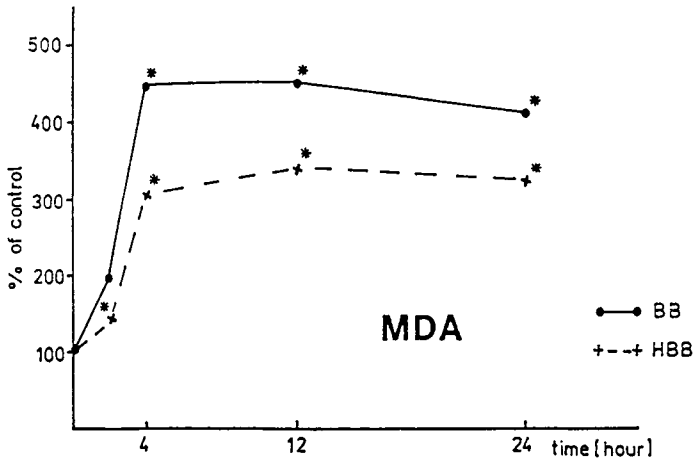


Fig. 3. The level of MDA in mice liver after single administration of 800 mg **1**/kg and 9000 mg **5**/kg.
* - significantly different from control animals
$\alpha = 0.05$

Similar decrease in GSH levels, increase in GPT activity and extent of necrosis, as after administration of **1**, can be observed, after dibromobenzenes injection (Fig. 4). The extent of the effect depended on the applied isomer and dose.

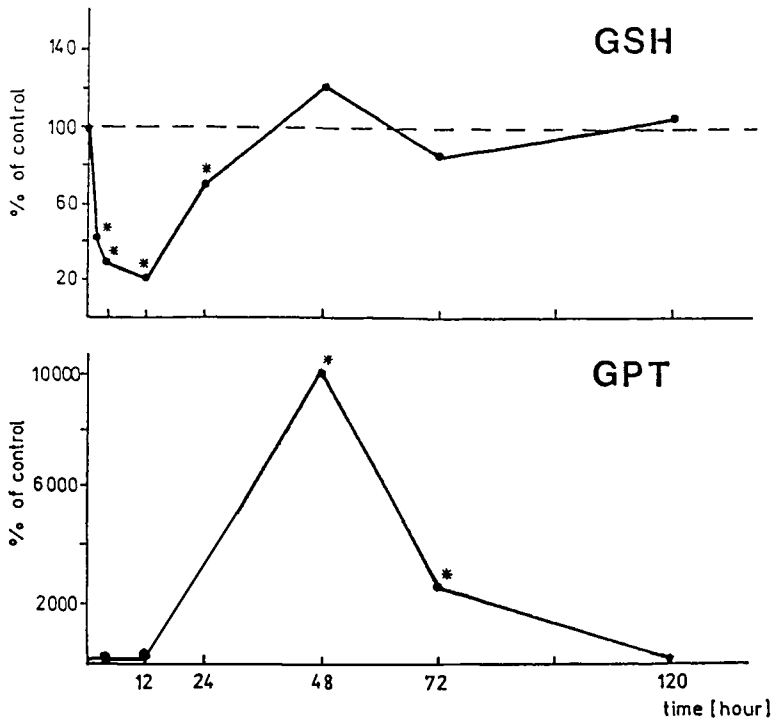


Fig. 4. The level of GSH in mice liver and the activity of GPT (SGPT) in serum after single dose of 2 (1000 mg/kg).
* - significantly different from control animals
α - 0.05

All three applied doses of 2 (250, 500 and 1000 mg/kg) (Fig. 4) and 3 (150, 300 and 600 mg/kg) caused a deep depletion in GSH concentration in the liver in short period of time after the administration (2-12 hours), reaching 10 % - 25 % of the control after the highest dose. In contrast, in the case of 4 (500, 1000 and 2200 mg/kg) the GSH decrease was rather small : the lowest concentrations were detected 12 hours after the injection of 2200 mg/kg, and they constituted approximately 60 - 70 % of the controls.

Most pronounced changes in GPT activity were detected after 2 (500 and 1000 mg/kg), 24-48 hrs after the administration (Fig. 4). 4 induced only slight nonsignificant increase in GPT activity after 2 hours.

The histopathological examination of mice liver performed after a single dose of dibromobenzenes shows that **2** and **3** isomers resulted in zonal coagulative or haemorragic necrosis. It affected from 25-50 % to over 50 % of the liver parenchyma (i.e. 4-5 arbitrary units). **4** caused necrosis of only individual hepatocytes.

Following administration of all dibromobenzenes, within a short period of time (2-4 hrs) a decrease of triglycerides (TG) concentration in the serum of mice was noted constituting approximately 30-60 % of the control values (Fig. 5). Dibromobenzenes caused an increase of MDA concentration in mice liver (Fig. 5).

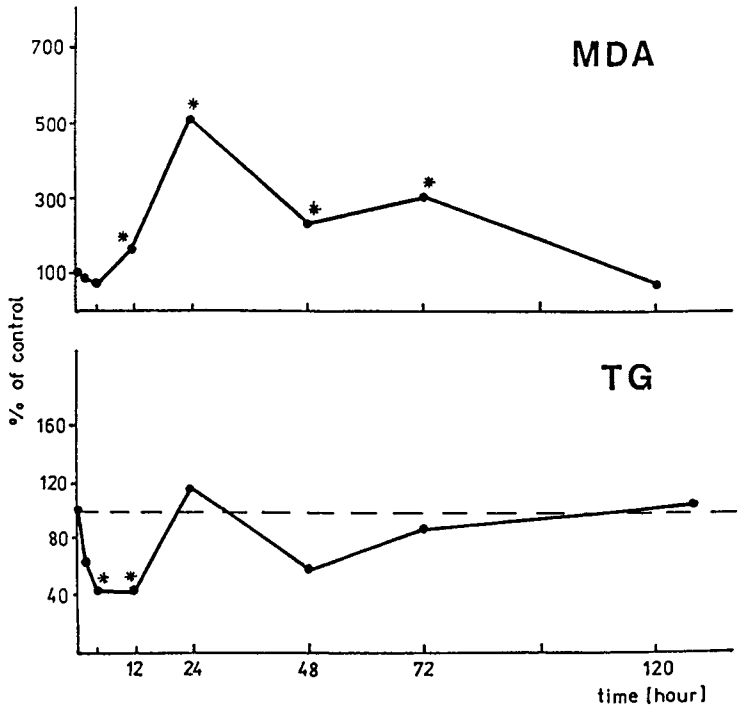


Fig. 5. The level of MDA in mice liver and the level of TG in mice serum after single dose of **2** (1000 mg/kg)
* - significantly different from control animals,
$\alpha = 0.05$

The activity of γ-GT in mice serum increased following the administration of bromobenzene, dibromobenzenes and hexabromobenzene. A pronounced significant increase after **5** and **1** was noted within a short period of time (2-4 hours). After injection of all dibromobenzenes the highest increase in γ-GT activity (3-6 fold) was detected after a longer period of time - 24-72 hours. Towards the end of the

experiment a decrease of γ-GT activity was observed, not attaining the control values.

During the second part of the experiment the examined compounds were applied repeatedly both to mice and rats. The same parameters, as after single administration were estimated in the serum and liver. Additionally, ALA-D and ALA-S, the two enzymes from haeme biosynthesis pathway were evaluated in the liver.

The studies on the effect of brominated aromatic compounds on the activity of ALA-D and ALA-S provide an introduction to the examination of porphyrogenic effect of these compounds. Disturbance in these enzymes as well as in URO decarboxylase activity according to some authors, might function as an introduction in development of liver porphyrias.

The activity of γ-GT as well as the level of TG and GSH after repeated administration of the studied compounds did not change. The increase of GPT activity in rats serum was observed only after 3 doses of tetrabromobisphenol A **6** (1000 mg/kg).

Following 7 doses of **1** (150 mg/kg), **5** (1500 and 3000 mg/kg), **6** (1100 mg/kg) and **4** (90 and 180 mg/kg) the 2-3 fold elevation of MDA concentration in rats liver was noted.

The maximum increase in ALA-D activity was observed following **1** (75 and 150 mg/kg), **2** and **3** (70, 135 and 270 mg/kg). The activities reached 140-150 % of the control values. In contrast, **6** caused statistically significant decrease of ALA-D activity. The highest increases in ALA-S activity were noticed after **2** (270 mg/kg), **4** (270 mg/kg) and **1** (300 mg/kg), and they constituted approximately 180-200 % of the control. Figure 6 presents the activity of ALA-D ans ALA-S in rats liver after administration of **1** and **2**.

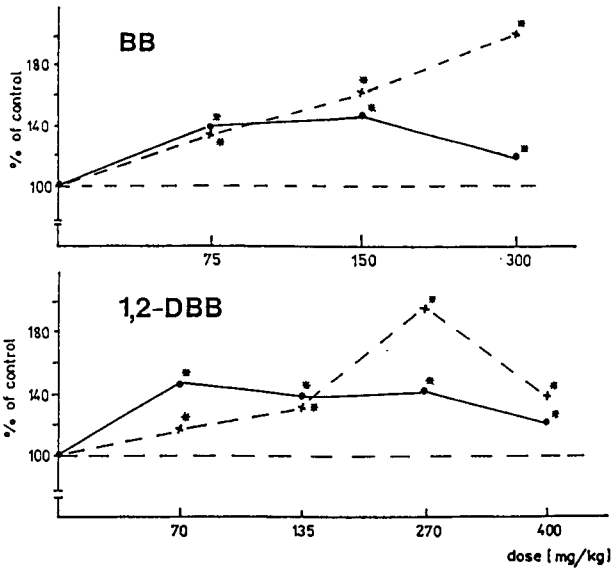


Fig.6. The activity of ALA-D (——) and ALA-S (x------x) in rats liver after seven doses of bromobenzene and 1,2-dibromobenzene.

* - significantly different from control animals

$\alpha = 0.05$

Histopathological examination of rats liver carried out after 7-fold administration of the studied compounds points out that the most visible pathological lesion is steatosis of all zones.

Repeated administration of **1**, **5** and dibromobenzenes to mice caused less pronounced changes in ALA-D and ALA-S activity, as compared to rats.

DISCUSSION

In the present study the investigations on the liver impairment in experimental animals, caused by bromobenzene, dibromobenzenes, hexabromobenzene and tetrabromobisphenol were described.

Bromobenzene, similarly to acetaminophen, is considered as model compound in liver necrosis (refs. 9-11, 20, 21). After the administration of these compounds, a considerable decrease in GSH levels, an increase in GTP activity in the serum and, histopathologically, necrosis of hepatocytes are observed.

A single dose of **2** and **3** administered to mice in different doses resulted in considerable decrease of liver GSH concentration shortly after the administration of both isomers, followed later, by a significant increase of GTP activity, as well as

histopathologically proved extensive necrosis. The dynamics of these changes was also comparable to the one following bromobenzene administration (refs. 22, 23). After **4** and **5** only slight decrease of GSH level was observed. No changes in GPT activity and no necrosis were present.

No changes in GTP and γ-GT activity were recorded after repeated administration of the above compounds. Also, histopathological examination did not point to liver necrosis. Similar phenomenon detected earlier after repeated administration of monobromobenzene, was interpreted as a result of damage of the microsomal enzymatic system responsible for the appearance of active metabolites (ref. 22).

Among aromatic bromine derivates, only polybrominated biphenyl is known to have a porphyrogenic effect (ref. 24). From scarce data about the toxicity of **4** and **5** porphyrogenic activity in the case of repeated administration could be expected (refs. 25,26). No data are available concerning the remaining compounds.

The results obtained after 7-fold administration of all studied compounds, suggest that these compounds cause disturbances in the heame biosynthesis pathway : changes in the activities of ALA-D and ALA-S were observed. Such results suggest the possibility of liver impairment of porphyrogenic type as a result of multiple administration of brominated compounds.

In conclusion, the obtained results suggest that the studied compounds differ from the point of view of acute hepatotoxicity. Only **2** and **3** after a single dose result in equal hepatotoxicity, as found previously for monobromo-benzene. The results obtained in part of experiments in which repeated doses were used, suggest the porphyrogenic properties of the compounds. This requires, however, an extended investigation with more specific indicators of such properties.

ACKNOWLEDGEMENTS

The author is indebted to Professor Jerzy K. Piotrowski for his interest in this study and discussion of the results.

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THE CHARACTERIZATION OF POLYBROMINATED DIPHENYL ETHER

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ABSTRACT

Commercially available polybrominated aromatic ethers have been analyzed by reversed phase high performance liquid chromatography. NMR spectra of material isolated by preparative methods served to identify the observed peaks as congeners of tetrabromo to nonabromo diphenyl ether. A bromination pathway was clearly indicated.

INTRODUCTION

In 1979, it was stated that polybrominated aromatic ethers have received little attention (ref. 1). That statement is still applicable. Analyses to characterize this class of commercial flame retardants have been performed using UV (refs. 1-2), GC (refs. 1-6), and GC-MS (refs. 1-4). The bromine content of observed peaks was measured by GC-MS, but no identification could be made. The composition of polybrominated (PB) diphenyl ether (DPE) was predicted from the expected relationship with polyhalogenated biphenyl, a class which has received extensive attention. NMR (refs. 3-6) was successfully used to identify relatively pure material which had six, or fewer, bromine atoms per molecule. A high performance liquid chromatography (HPLC) method described (ref. 1) was not as successful as GC. A reversed phase (RP) HPLC method was mentioned, but no further work was published.

The work presented here describes a RP-HPLC method for characterizing PB-DPE preparations. Components were purified by preparative RP-HPLC and identified by NMR. Components observed by GC under conditions similar to a published analysis (ref. 4), are identified by relation to the HPLC. A clear description of the bromination path can be made.

MATERIAL

Fire retardant preparations called Penta, Octa, high-melting Octa and Deca were obtained from the manufacturing division of Bromine Compounds Ltd.. Beer Sheva, Israel. The products are mixtures of PB-DPE, such that the percent bromine contained corresponds to a theoretical single component described by the product name. An authentic sample of hexabromo DPE was purchased from Matsunaga Chemical Industries CO. Ltd., Japan. All chromatographic solvents were purchased from BioLab Laboratories, Jerusalem, Israel. The NMR solvent was deuterated chloroform from Aldrich Chemical Co. Inc., Milwaukee, Wisc. Precaution against photodegradation was taken by wrapping samples in foil and storing in the dark.

METHODS

Analytical HPLC

A stainless steel column (4.6 mm internal diameter by 250 mm length) packed with 7 micron Zorbax ODS (Dupont) was equilibrated with 82 % Acetonitrile in water at a flow rate of 2.0 ml/min. provided by a Spectra Physics Model 8700 pump and controller. The effluent was monitored at 230 nm using either a Tracor UV-Visible detector Model 970A or a Jasco Uvidec UV detector Model 100-V. Peaks were recorded and calculated on a SpectraPhysics recording integrator, Model 4200 or Model 4270. Samples of 0.5 mg/ml in toluene were applied to the column automatically with a Micromeritics Autosampler Model 725 equipped with a 10 µl loop.

Preparative HPLC

A stainless steel column (10 mm internal diameter x 250 mm length) packed with 10 micron Techsil RP-18 (HPLC Technology Ltd., Cheshire, England), was equilibrated with 70 % Acetonitrile in water. After sample application, the desired separation was performed by changing the solvent composition to 100 % Acetonitrile and raising the flow rate from 4 ml/min to 6 ml/min, as required, using two HPLC pumps (Model 64) and a programmer (Model 50) from Knauer, Homberg, W. Germany. The effluent was monitored at 230 nm using a Jasco Uvidec UV detector Model 100-V equipped with a preparative cell. Chromatograms were recorded on a SpectraPhysics recording integrator Model 4100. Samples were applied as toluene solutions using a Rheodyne hand-operated valve (Model 7125)

equipped with a 100 µl loop. The fractions collected on an LKB SuperRac Model 2211 were dried and submitted for NMR spectra on a Bruker Model AM200.

Gas Chromatography

Gas chromatography analysis was performed on a Hewlett Packard GC Model 5890 equipped with a flame ionization detector and automatic injector 7673A.

The signal was recorded on a Hewlett Packard Integrator Model 3393A Integrator. Samples were injected onto a 30 m megabore column coated with 1.5 micron DB-5 purchased from J & W Scientific. The flow of nitrogen carrier gas was maintained at 30 cc/min. The column was equilibrated at 150°C. On injection of the sample, this temperature was maintained for five minutes followed by a programmed increase at a rate of 8°C/min. to a maximum of 300°C, which was maintained for 30 minutes.

Discussion

Samples of PB-DPE were subjected to RP-HPLC producing the chromatographic patterns shown in Figure 1. The two major peaks of Penta (Fig. 1A, peaks 1 and 2), were isolated by preparative HPLC and analyzed by NMR. The spectra (Table 1) were in excellent agreement with previously published data (refs. 3-6). The two HPLC peaks were identified as 2,2',4,4' tetrabromo DPE and 2,2',4,4',5 pentabromo DPE, respectively.

A purchased sample of hexabromo DPE chromatographed coincident with peak 3 of Figure 1B. The NMR data (Table 1) agreed with published data (refs. 3-6) and was consistent with the structural assignment of 2,2',4,4',5,5' hexabromo DPE.

The structure of the last eluting peak (Fig. 1D, peak 10), structure is easily deduced to be 2,2',3,3',4,4',5,5',6,6' decabromo DPE from the bromine content of the pure sample, lack of proton spectrum and long retention time. Indeed, a recrystallized standard serves as reference material for a quantitative HPLC assay to be described elsewhere.

It had been observed that Octa is predominantly heptabromo DPE (ref. 3). The predominant peak (Fig. 1B, peak 4) is here identified as the isomer 2,2',3,4,4',5',6 heptabromo DPE by interpreting the NMR spectrum (Table 1) of material isolated preparatively.

A - Penta;

B - Octa;

C - High-melting Octa;

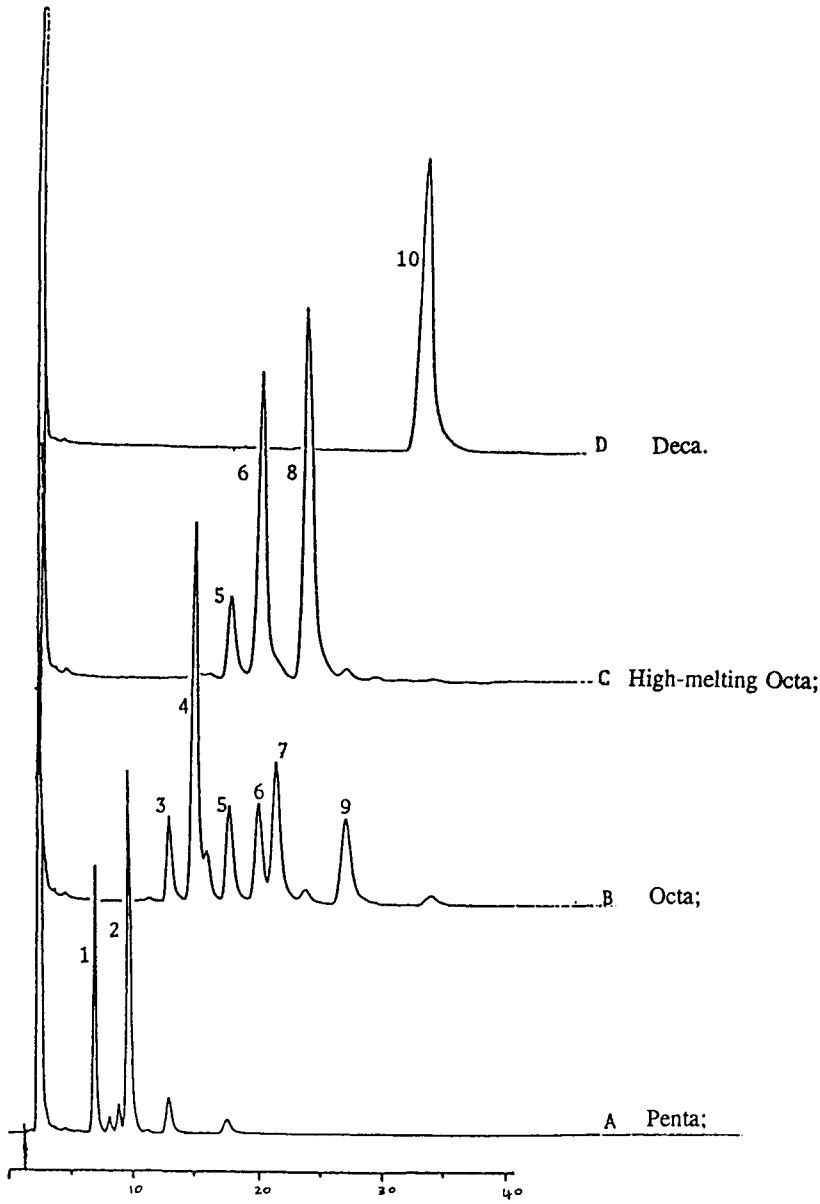

Figure 1. HPLC Chromatogram of PB-DPE Fire Retardants : For conditions, see text.

Table 1. The 200 MHz proton NMR Spectra of Peaks Isolated by Preparative Chromatography

HPLC Peak[a]	Chemical Shift[b], Proton[c] (δ)					
	3	5	6	3'	5'	6'
1	7.79(d)	7.37(q)	6.71(d)	7.79(d)	7.37(q)	6.71(d)
2	7.88	---	7.00	7.81(d)	7.42(d)	6.79(d)
3	7.90	---	7.08	7.90	---	7.08
4	7.98	---	---	7.90	---	6.58
5	---	---	---	7.88	---	6.62
6	8.00	---	----	---	---	6.60
7	7.85	---	---	7.85	---	---
8	---	---	---	---	---	6.63
9	---	---	---	7.81	---	---
10	---	---	---	---	---	---

[a] See Figure 1

[b] In deuterated chloroform; internal standard tetramethylsilane

[c] The position number assignments in the table are for convenience and are arbitrarily fixed to the position numbering of 2,2',4,4'-tetrabromodiphenyl ether.

Of the five remaining peaks (Figure 1B, peaks 5 to 9), three (peaks 5,7 and 9), were easily separated from the octa samples by preparative HPLC, and the two remaining (peaks 6 and 8) were isolated from high-melting (Figure 1C).

Peak 5 revealed two types of protons in the NMR spectrum (Table 1). Based on comparison with previous NMR assignments, peak 5 is 2,2',3,4,4',5,5',6-octabromo DPE, where the protons are on the same ring. Peak 6 also revealed two types of protons (Table 1). With similar reasoning the structure is 2,2',3,3',4,4',5',6 octabromo DPE, where the protons are on separate rings.

Peaks 7, 8 and 9 (Figures 1B and 1C) each gave only one signal in the NMR. The NMR signal of peak 7 at 7.85 is very close to that of peak 9 (Table 1). Since it elutes the earliest, Peak 7 is probably the remaining octabromo isomer and is assigned the symmetrical structure 2,2',3,3',4,4',6,6'-octabromo DPE. The longer retained peak 9 is therefore assigned the structure 2,2',3,3',4,4',5,6,6'-nonabromo DPE. Peak 8 must also be a nonabromo isomer and the assignment of the structure 2,2',3,3',4,4',5,5',6 nonabromo DPE is consistent with th NMR signal (Table 1) observed and the assignements given to peaks 5 and 6.

A GC trace of Octa, under conditions similar to those described by Timmons and Brown (ref. 4), closely resembled the published chromatogram for trace impurities in Deca. Material isolated from HPLC peak 7 (Figure 1B) eluted from the GC (Figure 2) in a position corresponding to one of the octabromo isomers in the published work. This agrees with the assignment of peak 7 as an octabromo isomer in this work. Material isolated from HPLC peaks 8 and 9 (Figure 1B and

1C) eluted from the GC (Fig. 2) in positions corresponding to the two nonabromo isomers of the published work.

A - Octa;

B - High-melting Octa;

C - Deca;

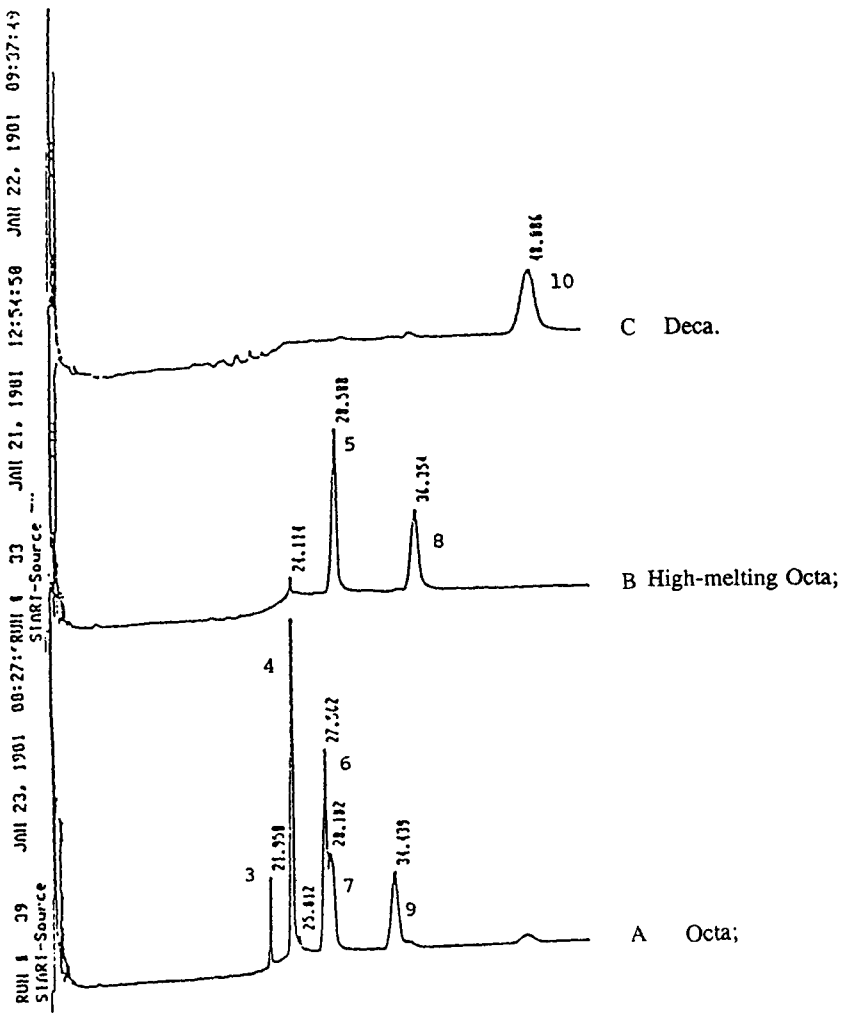

Figure 2. GC of PB-DPE Fire Retardants :
GC conditions are given in the text. Peak numbering refers to the HPLC peaks in Table 1.

A third nonabromo isomer (ref. 4) was absent from the BCL material. This may have been a breakdown product in their Deca sample, which has been noted to be unstable to light (ref. 5). The elution order of the Octa and Nona isomers on GC was 6,7,5,9,8 (numbering according to Fig. 1).

No brominated diphenyl was observed in any of the BCL samples at the analyzed levels.

Since peak 8 is the largest one in the HPLC tracing (Figure 1C), high-melting Octa may be aptly named "Nona". It was predicted that this isomer would be the predominant isomer of nonabromo DPE in Octa[1]. That prediction is apparently incorrect.

Consistent with the foregoing data, the bromination of DPE may be described as proceeding according to the scheme shown in Figure 3.

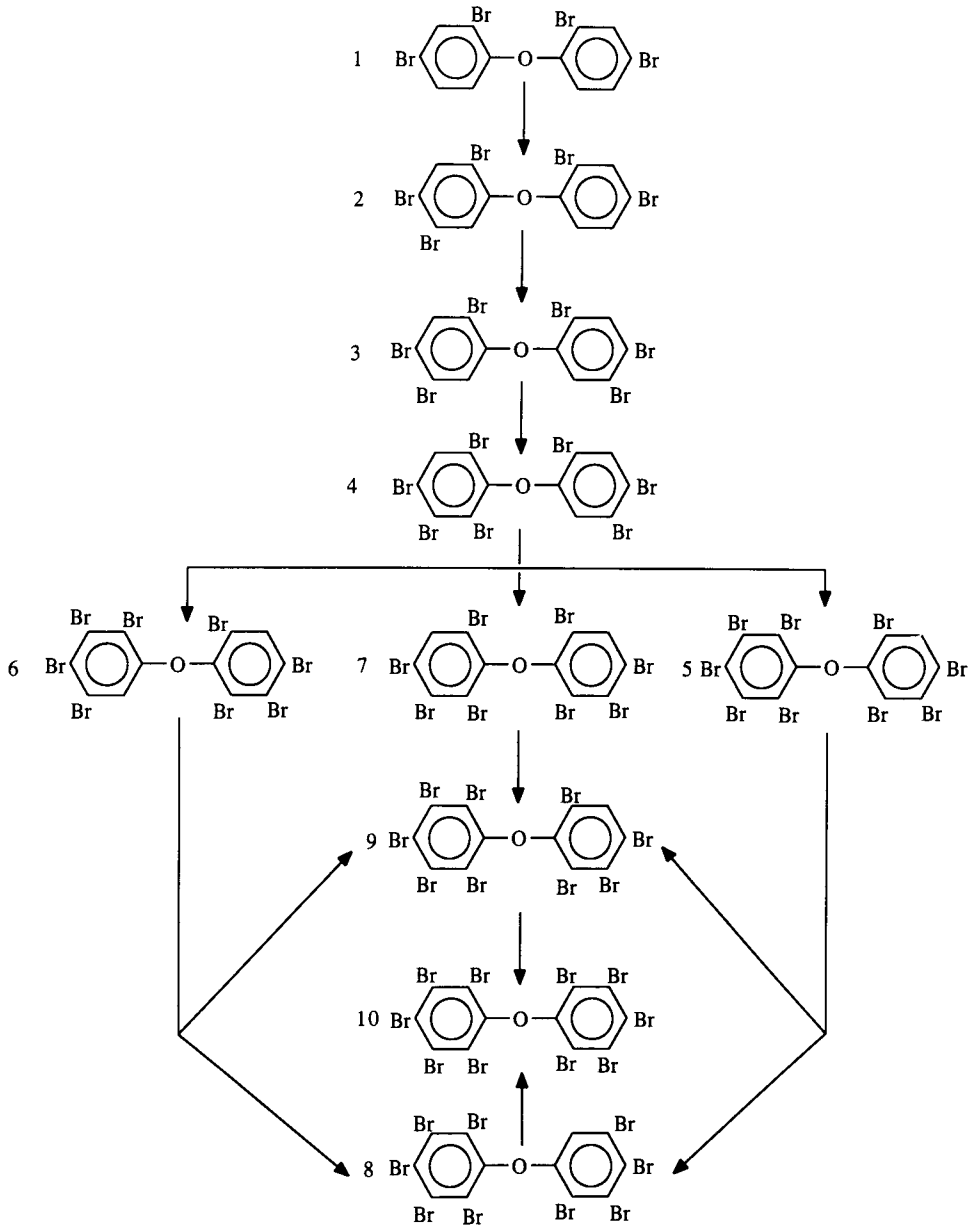

Figure 3. Bromination pathway from DPE to decabromo DPE.

The ortho para directiveness of the ether linkage is weakened by the addition of two bulky bromine atoms to each ring. Steric considerations become more significant. Positions 5 and 5 ' become the more reactive positions rather than 6 and 6'. After a single bromine enters position 6, to form heptabromo DPE, the next bromine enters any of the remaining positions to form the various octabromo isomers. Two of these isomers (Figure 1C, peaks 5 and 6) have positions ortho and meta to the ether linkage available. The octabromo isomers identified are consistent as being possible intermediates between the heptabromo isomer and the two nonabromo components found. The absence of the third possible nonabromo isomer is also consistent with this scheme. The ninth bromine will enter the meta position giving rise to the nonabromo isomer, peak 8. The symmetrical octabromo isomer in peak 7 can give rise to the nonabromo isomer of peak 9 only.

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ANALYSIS OF PENTAERYTHRITOLS AND BROMINATED DERIVATIVES

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ABSTRACT

The analysis of pentaerythritols and brominated derivatives, which are fire retardants, may be performed by a number of techniques, some of which will be discussed here. Each procedure suffers from different drawbacks. The method chosen must answer the specific need of the analysis. We use the following abbreviations.

METHODS

High performance liquid chromatography (HPLC)

A stainless steel column (4.6 mm internal diameter by 250 mm length) packed with 4 micron Zorbax Octadecylsilane (ODS) (Dupont) was equilibrated with 78 % acetonitrile in water at a flow rate of 2.0 ml/min provided by a Spectraphysics, model 8700, pump and controller. The effluent was monitored at 215 nm using a Jasco Uvidec 100 V ultraviolet detector. Peaks were recorded and calculations performed by a Spectraphysics recording integrator, model 4270. Samples, containing 5 mg/ml of material dissolved in p-dioxane, were applied to the column automatically with a Micromeritics autosampler, model 725, equipped with a 10 microliter loop. Some analyses were performed on a Hewlett-Packard HPLC, model 1090, equipped with a diode array detector.

Gas Chromatography (GC)

A Hewlett Packard gas chromatograph, model 5890A, equipped with a flame ionization detector and a Hewlett Packard integrator, model 3396 series 2, were used.

Differential Scanning Calorimetry (DSC)

Dynamic calorimetric measurements were made on 10 mg samples in sealed aluminum pans over the temperature range 50°C to 220°C at 10°C/min using a Mettler thermoanalytical system consisting of a DSC, model 20 and processor, model TC-10A, which performed the data handling.

TEXT

The scope of my comments will cover not the development of analytical methods but rather the process of choosing methods which give useful answers to the questions posed by the research chemist, the process engineer or the product marketing manager. The analytical chemist is always faced with the paranoia causing problem of not being able to be confident in a purity measurement until it can be shown that impurities do not interfere.

Figure 1 shows the condition of materials submitted for analysis at various stages of becoming a product. Complications arise from uncertainties in sampling and of course in separating impurities. The availability of an instrument can effect the decision of which analysis to perform.

RAW MATERIAL
- Reasonably Pure
- Occasional interfering impurity

REACTION INTERMEDIATES
- Mixtures
- Phases

FINAL PRODUCT
- Reasonably Pure
- Impurities

Fig. 1. The condition of materials submitted for analysis.

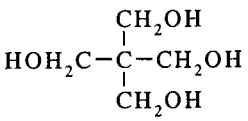
Considerations of turn around time for the analysis, the statistical confidence level and the specificity required also play a part in the decision. Even a so called quick and dirty method can become quantitative to an acceptable extent once conditions are standardized.

Different methods can be used, for example, HPLC, GC, NMR, IR, Titration...

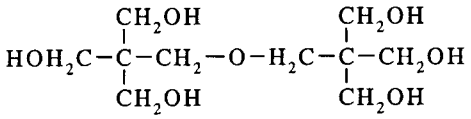
When performing the initial development work it is best to try to obtain corroboration of one method by another. This helps avoid the paranoia.

The reaction sequence to be used as an example will be the bromination of polyhydroxyl compounds by exchange with bromide ion (eqn. 1). In particular, at Bromine Compounds, we are concerned with the bromination of pentaerythritol **1** and dipentaerythritol **2**.

$$R\,(OH)n \longrightarrow R\,(OH)n\text{-}t\,Br_t \qquad (1)$$



1



2

The raw materials are usually mutually contaminated to about 5 %. Thus, DSC can be ruled out. The compounds are made by aldol condensations and cross Canizzaro reactions between acetaldehyde and formaldehyde. An elegant method of distinguishing between the two raw materials takes advantage of the 10 fold solubility difference between the two in methanol and water.

Temperature programmed GC (Fig. 2) separates these components as well as a cyclic formal. The mono, di and tri brominated products of **1** require higher temperatures to elute in a reasonable time; more than the column can withstand. TMS derivatives do not require temperatures quite so high (Fig. 3). Using this technique for quantitation, however, is complicated by the decreasing sensitivity of the FID to increasing bromine content.

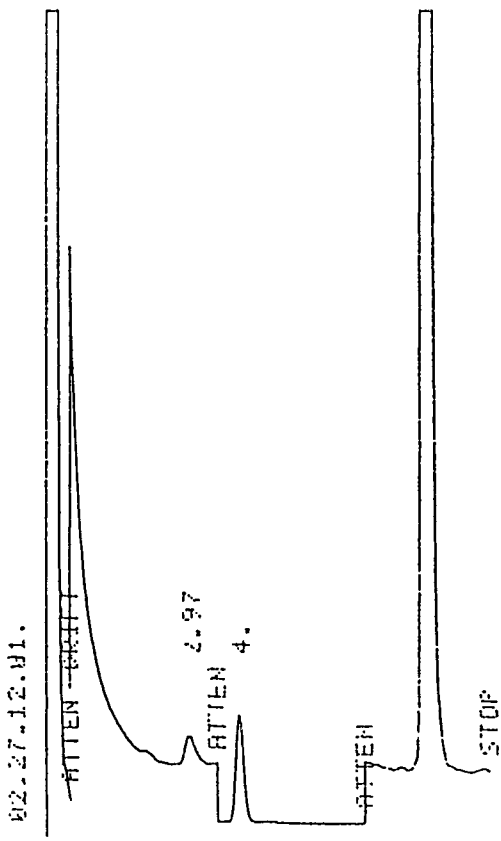


Fig. 2. Temperature programmed GC of raw material

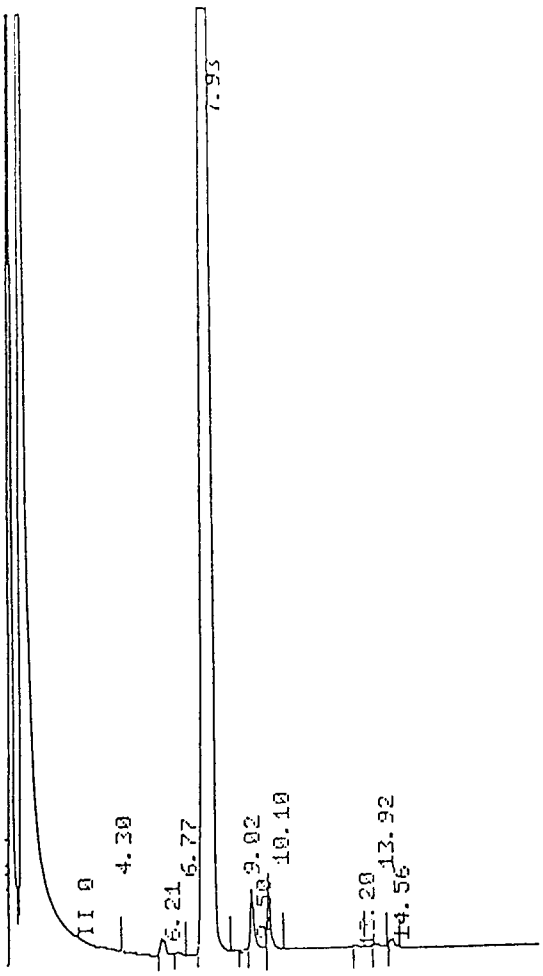
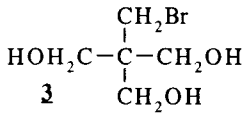


Figure 3. GC of TMS derivatives of bromination products

The intermediates of bromination of pentaerythritol are **3**, **4** and **5**.



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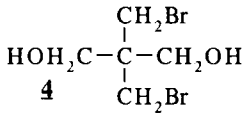

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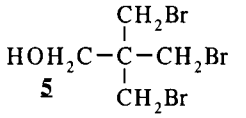

5

HPLC of these brominated hydroxy compounds is made difficult by the wide variation in polarity and molecular weight, requiring the use of solvent gradients, and by the fact that the compounds have very weak chromophores, requiring the use of the refractive index detector or very low wavelengths on the UV detector Figure shows an analysis of **5**. Most synthesis chemists believe their samples to be of high purity. Figure 5 is the same sample at a 10 fold concentration. Figure 6 shows a 25 fold concentration. One can almost provide the research chemist any answer he wants.

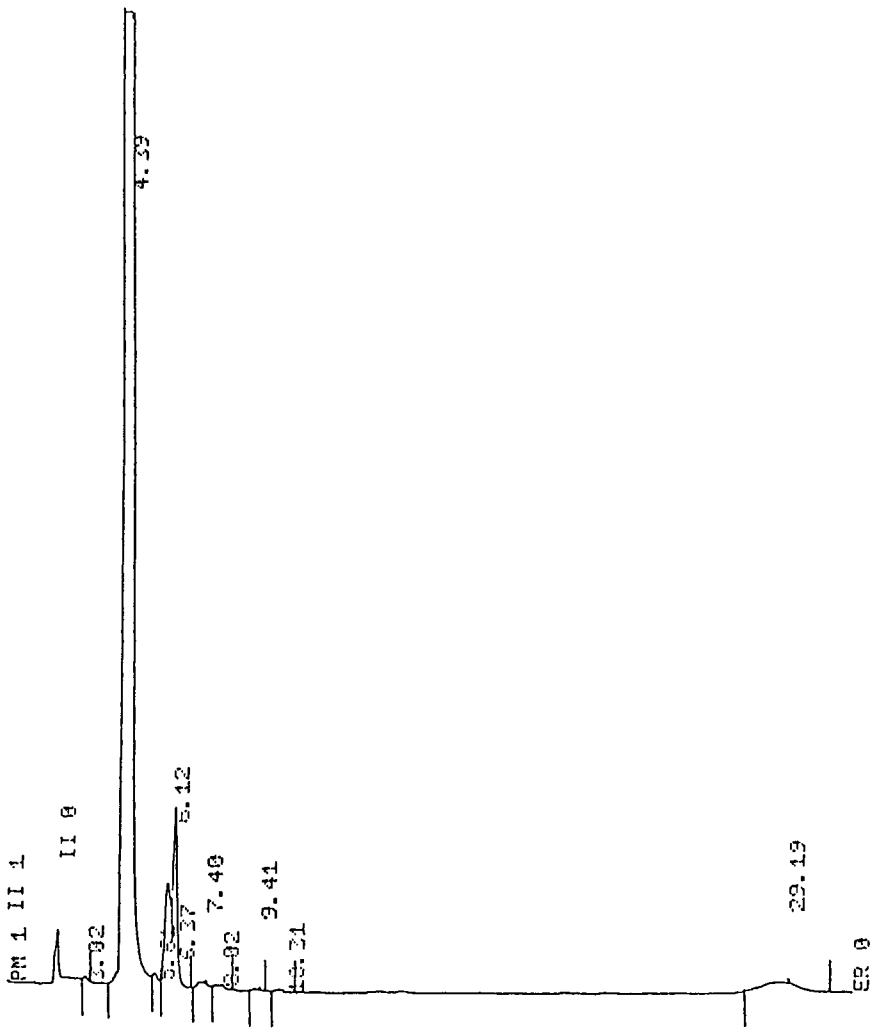

Fig. 4. HPLC analysis of **5**

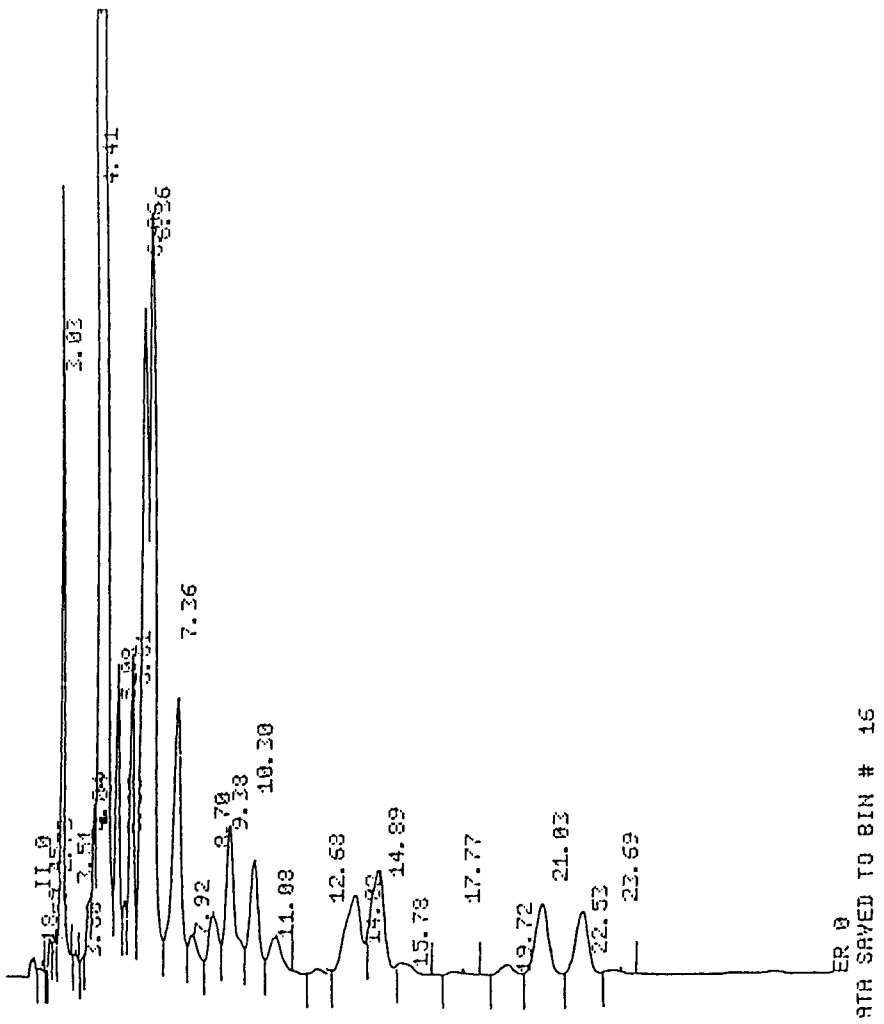

Fig. 5. As in Figure 4 with ten fold concentration

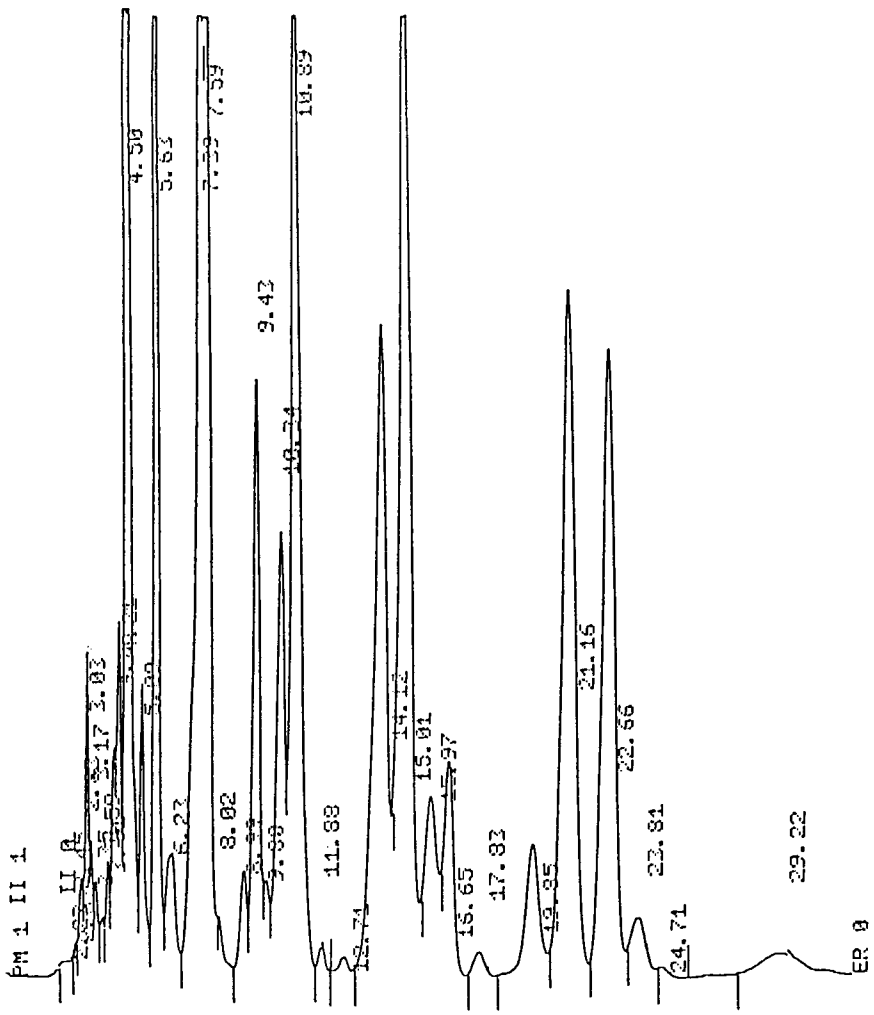

Fig. 6. As in Figure 4 with twentyfive fold concentration

Esterification of the hydroxyl groups with a chromophore contributing acid levels the polarity effects and strengthens the detectability. The method even separates mixed bromo-chloro compounds (Fig. 7). We see the separation of the dinitrobenzoate esters of trichloropentaerythritol (6.67 min.), monobromodichloropentaerythritol (7.35 min.), dibromomonochloropentaerythritol (8.11 min.), **5**, **4** and **1** (8.99, 10.25 and 11.71 min.), in that order.

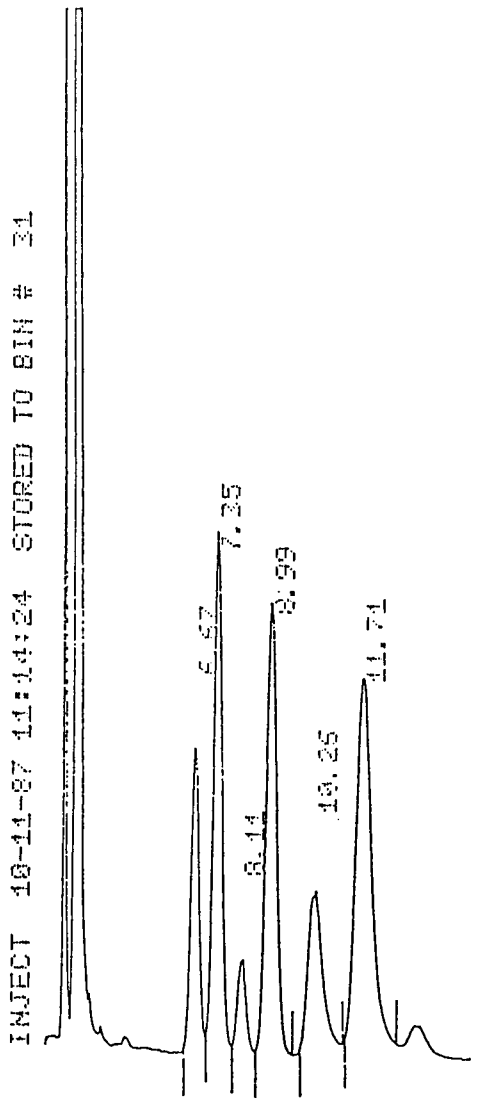

Figure 7. HPLC of the dinitrobenzoylated derivatives of mixed chlor-bromo analogues of TRINOL

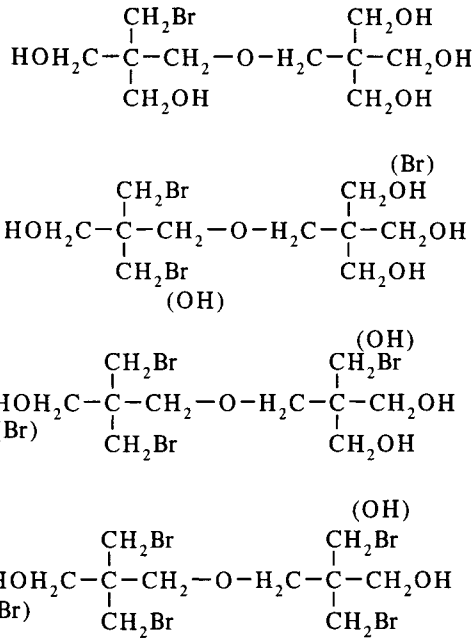

Fig. 8. The intermediates of the bromination of dipentaerythritol

Fig. 9. Differential scanning calorimetry of.

The intermediates of the bromination of dipentaerythritol **2** (Fig. 8) can be treated in the same way. The chromatogram can be expected to be more complex.

Differential Scanning Calorimetry (Fig. 9) can be used to evaluate the purity of tetrabromodipentaerythritol, a tetrabrominated derivative of dipentaerythritol. Even so, the validity of the results depends on the purity of the sample. The results shown here should be considered extremely borderline. The brominated derivatives of the pentaerythritols cannot be analyzed with this technique because of the inherent limitations of DSC.

CONCLUSION

To summarize then, the choice of method should be dictated by the real needs of the submitter of the sample and not by the fanciness of the available instrumentation.

AUTHOR INDEX

SUBJECT INDEX

C

D

E

F

G

H

I

M

N

O

P

Q